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NOCARDIOSIS

Clinical, Bacteriologic and Pathological Aspects

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NOCARDIOSIS is an acute or chronic infection that may closely resemble other suppurative conditions due to such varied agents as klebsiella, pasteurella, salmonella, malleomyces and actinomyces. The cattle studied by Nocard[1] were suffering from multiple abscesses, draining sinuses, emaciation and pulmonary involvement with fatal termination. The disease occurs in other animals[2-4] and is frequently misdiagnosed as actinomycosis,[5] although the condition reported by Nocard is quite different from actinomycosis, as described by Harz[6] and Bollinger.[7] The causative organism is also quite different from the actinomyces isolated by Wolff and Israel[8] but it probably is closely related to, if not identical with, the aerobic organism described by Bostroem.[9] The differentiation between actinomyces and nocardia has been set forth clearly by Waksman and Henrici[10] and is the basis of the classification used in *Bergey's Manual of Determinative Bacteriology*,[11] which lists 33 species of nocardia.

The following cases are presented to illustrate the importance of recognizing early whether a pulmonary infection is due to nocardia, so that when nocardiosis is present, proper chemotherapy may be administered promptly to save a life or prevent the crippling effects of metastatic lesions in vital organs.

CASE REPORTS

CASE 1. A 26-year-old physician registered at the Mayo Clinic in 1944 with a clinical diagnosis of "arrested minimal pulmonary tuberculosis" based on a negative Mantoux reaction in 1940 that became positive in 1942 and on a roentgenogram in November, 1943, that showed a lesion in the right upper lobe. Repeated bacteriologic studies were negative for acid-fast bacilli. In June, 1944, x-ray examination showed that the lesion had enlarged and was probably excavating. Further studies in the sanatorium were negative for acid-fast bacilli. In the fall of 1945, fluid began to accumulate in the right pleural space. Numerous smears and cultures of the fluid were negative for acid-fast bacilli. The patient was treated with penicillin, without improvement. In March, 1946, a culture of the pleural fluid was positive for *Nocardia asteroides*. Growth of the organism was not inhibited by penicillin but was inhibited by a 1:80,000 dilution of sulfadiazine. Sulfadiazine was given orally and intrapleurally; the patient recovered and was back at work in 5 months. He has remained well to date.

CASE 2. A 7-year-old boy was brought to the clinic on March 7, 1946, because of cough and persistent fever. On December 17, 1945, the parents had noted a sudden high fever (temperature of 105°F.). About 2 weeks later a cough productive of 120 to 240 cc. (4 to 8 ounces) of purulent sputum daily had begun. The temperature had persistently risen to 104 or 105°F. twice daily in spite of repeated courses of penicillin. On arrival the patient appeared acutely and critically ill. A roentgenogram of the thorax showed extensive bilateral pneumonitis, with a suggestion of multiple abscesses in the left lung (Fig. 1). A review of roentgenograms made at home disclosed that the process had begun on the left side and had progressed before extending to the right lung. Examination of the blood revealed a red-cell count of 1,940,000, with a hemoglobin of 7.5 gm. per 100 cc., and a white-cell count of 28,600, with 97 per cent neutrophils. Penicillin was administered, but the temperature continued its rises, to 104 to 106°F., once or twice daily. The patient failed rapidly and died 5 days after admission. Autopsy disclosed organizing pneumonia and multiple pulmonary abscesses from which *N. asteroides* was cultured.

CASE 3. A 42-year-old dentist with Cushing's syndrome underwent bilateral exploration of the adrenal glands. Half the right adrenal gland was removed, and the patient was dismissed on November 7, 1947. On January 29, 1948, he was readmitted to the clinic with cough productive of thick, yellow sputum and hemoptysis. Roentgenograms showed an area of pneumonia in the right lower lobe (Fig. 2), and cultures of the sputum were positive for *N. asteroides*. When the patient was treated with 8 to 10 gm. of sulfadiazine daily, the cough and hemoptysis soon ceased, and x-ray examination demonstrated rapid regression of the intrapulmonary process. In December, 1948, he died at home, presumably of Cushing's syndrome.

CASE 4. A 57-year-old woman came to the clinic on May 14, 1949, because of fever, anemia and rapid pulse. In December, 1947, she had been found to have pulmonary tuberculosis and had been treated with rest in bed. Streptomycin was given for 6 weeks, but treatment had to be discontinued because of blurred vision. In March, 1949, she had 1 episode of "flu," with cough and production of yel-

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low sputum, lasting 2 weeks. In April she had had daily rises of temperature up to 103°F.

Examination at the clinic disclosed tenderness of the abdomen and x-ray evidence of a cavity in the left apex. Laparotomy on June 3 showed numerous tubercles in the peritoneum and omentum that were proved to be tuberculous by guinea-pig inoculation. Rapid improvement followed treatment with dihydrostreptomycin and para-aminosalicylic acid, and the patient was discharged on September 3.

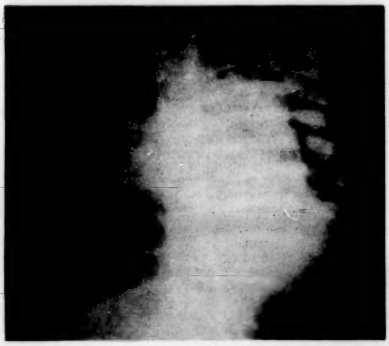

FIGURE 1. *Extensive Bilateral Pneumonitis in Case 2.*

On November 1 she had another attack of "flu" with severe cough, production of gray sputum, hoarseness and pain in the right side of the thorax. She returned on December 5, in critical condition, with x-ray evidence of numerous lesions throughout both pulmonary fields (Fig. 3); she was thought to have bronchial dissemination of the tuberculosis. The white-cell count was 36,000, and the appearance of the sternal bone marrow suggested monocytic leukemia of the Naegeli type. She was given dihydrostreptomycin and urethane, but she died on December 21.

FIGURE 2. *Pneumonitis of the Right Lower Lobe in Case 3.*

At autopsy, the following anatomic diagnoses were made: organizing bronchopneumonia of the lungs, with multiple abscesses of the right upper lobe due to *N. asteroides* (Fig. 4 and 5); chronic bronchiectasis (aspergillus present in the left upper lobe); evidence of former abdominal exploration for tuberculous peritonitis; healing ulcerative enteritis (tuberculosis with multiple strictures); hypertrophy of the liver (weight, 2170 gm.) and spleen (weight, 385 gm.) (acute monocytic leukemia found clinically); and hemangioma of the right cerebellar hemisphere.

CASE 5. A 57-year-old woman came to the clinic on June 10, 1949, because of frequent colds and blood-streaked nasal discharge that she had had for 6 months. She had had purulent otitis media, which had been treated by surgical drainage in March. In May, she had had conjunctivitis, and x-ray examination had shown "spots on the lung." She had been hospitalized, had had night sweats and had become very weak.

The temperature was 100°F. There was bilateral nerve deafness. The white-cell count was 12,400, and the sedimentation rate 129 mm. in 1 hour. Grade 2 hematuria and pyuria were found. There was roentgenologic evidence of infiltration in the right-middle-lung field and of 2 small areas of pneumonitis in the left lung. A tuberculin test with second-strength purified-protein derivative gave a Grade 2 reaction (on a basis of 1 to 4). Cultures of the sputum were negative for acid-fast bacilli but positive for *Candida albicans*. Cultures of the urine were positive for *Escherichia coli*. No positive diagnosis was made and the patient was sent home to await results of cultures of the sputum, gastric washings and urine.

On October 8 she returned, critically ill, with spastic quadriplegia and x-ray evidence of a lesion 4 cm. in diameter in the upper lobe of the right lung (Fig. 6). The white-cell count was 18,300, the sedimentation rate 140 mm. in 1 hour, and the blood urea 309 mg. per 100 cc. Autopsy, however, disclosed pulmonary and cerebral abscesses from which *N. asteroides* was cultured.

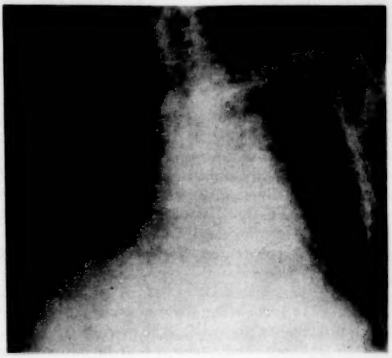

FIGURE 3. *Diffuse Bilateral Pulmonary Lesions in Case 4.*

CASE 6. A 53-year-old woman, who came to the Mayo Clinic on June 22, 1953, had been ill since January, with daily fever (temperature of 101°F.) and a cough productive of 2 or 3 tablespoonfuls of thick, white sputum daily. The condition did not respond to treatment with either penicillin or streptomycin.

X-ray examination disclosed pneumonia in the basal segments of the right lower lobe (Fig. 7). The white-cell count was 9000, and the sedimentation rate 78 mm. in 1 hour. Cultures of the bronchial secretions from the right lower lobe were positive for *N. asteroides*. Exploratory craniotomy performed because of headache, drowsiness and weakness of the left side of the body demonstrated a multilocular brain abscess. Cultures of the pus were positive for *N. asteroides*.

Treatment with sulfadiazine was started on July 3, the

day *N. asteroides* was reported from the bronchial washings and 6 days before craniotomy. The patient gradually improved, and the lesion in the right lower lobe disappeared. She was discharged to the care of her home physician and home hospital on September 6. She returned on November 11, critically ill, with headache, fever, weakness of the left side of the body, convulsions and unresponsiveness, and died on December 11.

At autopsy the following anatomic diagnoses were made: previous right frontoparietal craniotomy and resection for a multilocular abscess of the right frontoparietal parasagittal region of the brain (*N. asteroides*); residual abscesses of the left parietal lobe of the brain (Fig. 8 and 9); edema of the brain, with notching of the left peduncle; abscesses, with scarring, of the right lower lobe of the lung (*N. asteroides?* — cultures negative); thrombosis of the left iliac and femoral veins, with edema of the left leg.

Case 7. A 15-month-old boy was brought to the clinic on January 14, 1953. During the first 6 months of life he had had diarrhea and a skin rash. In September, 1952, at 1 year of age, he began to have a cough and fever (temperature of 101°F.), and had a generalized convul-

Figure 4. *Bronchiectasis, Emphysema of Both Lobes and Abscesses of the Upper Lobe of the Right Lung Due to Nocardiosis (Case 4).*

sion. Episodes of cough and fever continued, and a diagnosis of pneumonia was made in December, 1952. In spite of treatment with oxytetracycline, chlortetracycline and cortisone, his illness gradually worsened.

X-ray examination revealed bilateral pneumonia (Fig. 10). The white-cell count was 15,000. The duodenal contents demonstrated a normal amount of trypsin. Tuberculin, histoplasmin and coccidioidin skin reactions were negative. Cultures of swabs from the pharynx were positive for *Aerobacter aerogenes* and *C. albicans*. Fluctuations of temperature up to 104°F. prevented bronchoscopy as a means of obtaining suitable material for bacteriologic study. Chlortetracycline, penethamate hydriodide and erythromycin did not control the infection, and the patient died on February 4, 1953. Autopsy revealed multiple abscesses in both lungs, the brain, the pancreas and the intercostal muscles. Cultures of the abscesses showed *N. asteroides*.

Discussion

Clinical and Roentgenologic Considerations

In each of the cases presented above, pulmonary disease was the initial problem. This was usually manifested by cough of varying degrees of severity.

Figure 5. *Abscess of the Upper Lobe of the Right Lung (Brown–Gram Stain X 1,400) Due to Nocardiosis (Case 4). Note the branching mycelia.*

The sputum was usually thick, sticky and either mucopurulent or purulent. The temperature varied from normal to daily elevations up to 105°F., and the

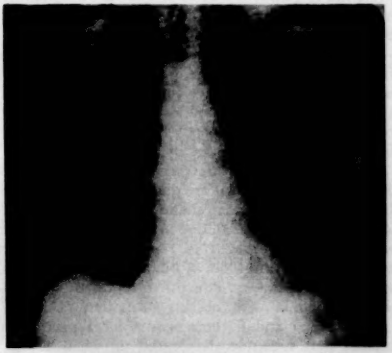

Figure 6. *Large Mass in the Right Lung, with Hazy Infiltration of the Left Lung, in Case 5.*

patients exhibited variable degrees of systemic reaction.

The portal of entry of the organism was thought to be the respiratory tract in each case, and in most cases the prominent symptoms were related to the

lungs. A review of the literature shows that *N. asteroides* has been cultured, however, from almost every part of the body, including the brain, lymph nodes, skin and subcutaneous tissues, bone, kidney and various portions of the alimentary tract. Nocardiosis has occurred after dental extractions,[12,13] and the possibility of the alimentary tract as a portal of entry has been emphasized.[14] It is possible, then, for the organism to gain entry through a break in the mucosa or even from a break in the skin, and from there to be spread to other portions of the body.

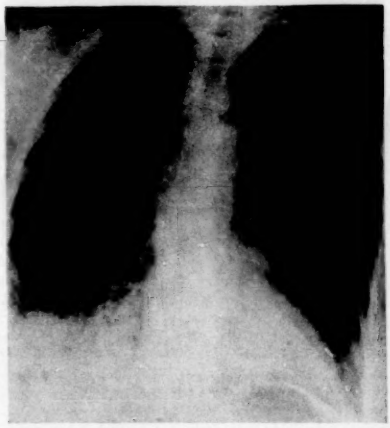

FIGURE 7. *Pneumonitis in the Basal Segments of the Right Lower Lobe in Case 6.*

The central nervous system has been the most frequent extrapulmonary site of the disease. There was definite clinical involvement of the nervous system in 2 of the cases reported above, with intracerebral abscess formation. The pleural space was involved in 1 case, with empyema.

A review of the roentgenograms in these 7 cases discloses no features that are diagnostic of nocardiosis. In each case, abnormal shadows were present, but they varied from a small one in an upper lobe, which was mistakenly thought to represent active tuberculosis (Case 1), to those of bilateral patches of consolidation, which were thought to represent suppurative pneumonia with abscess formation (Case 2).

In Cases 3 and 6 there was a local pneumonic process that subsequently cleared up when the patient was treated with sulfadiazine. In Cases 2 and 5 the disease was disseminated when the patients were first seen whereas dissemination occurred during the period of observation in Case 4. In Case 1 pleural fluid began to accumulate after pneumothorax was initiated for therapeutic purposes.

It seems that the disease begins in the lung as a local area of pneumonia, and that it may progress by dissemination or by the formation of an abscess. Such a pattern is certainly not diagnostic from the roentgenologic point of view, since it may be produced by other infectious processes. The x-ray examination is useful in revealing the presence of the disease in the lung, in determining its location and extent and in following its course, but in no way can it enable the physician to diagnose the specific etiologic agent. The differential roentgenologic diagnosis must include tuberculosis, histoplasmosis, acute bacterial pneumonia and possibly primary carcinoma (Case 5).

The only diagnostic laboratory procedure is bacteriologic demonstration of the organism. As is to be expected in any infectious process, anemia, leukocytosis and increase of the sedimentation rate are common. In 1943, Drake and Henrici[15] reported the production of an allergic state by intratesticular injection of oil suspensions of live organisms into guinea pigs and rabbits. They then demonstrated the allergic state by intracutaneous injection of a crude extract of powdered organisms, which produced swelling with an area of central necrosis similar to the tuberculin reaction. There was no cross reaction with tuberculin. We have had no experience with this test and cannot testify to its validity.

FIGURE 8. *Confluent Abscesses of the Left Parietal Lobe of the Brain Due to Nocardiosis in Case 6.*

Nocardiosis should be suspected when an acute or subacute pneumonitic process does not respond promptly to treatment with the usual antibiotics such as penicillin or tetracycline compounds. Even

though the roentgenologic appearance most commonly resembles that of tuberculosis, the clinical course is usually more acute than that of tuberculosis, and the sputum is more frequently thick, sticky and purulent. The disease clinically may resemble other mycotic diseases such as coccidioidomycosis, blastomycosis, histoplasmosis and cryptococcosis. When there is unilateral pulmonary infiltrate, neoplasm must frequently be considered. Nocardiosis further mimics bronchogenic carcinoma in frequency of intracerebral metastasis.

It is apparent that the diagnosis of nocardiosis depends on demonstration of the organism in the bacteriologic laboratory. It is the responsibility of the clinician, however, to be alert to the diagnostic possibilities, to obtain proper material for culture by the bacteriologist and to request that cultures for fungi be performed.

Recognition of the organism is exceedingly important because an effective chemotherapeutic agent is available. Sulfadiazine was used in 3 of the cases reported above, and in each it was effective against

FIGURE 9. *Abscesses of the Brain (Hematoxylin and Eosin Stain X 100) Due to Nocardiosis in Case 6. Note the daughter abscesses and lack of encapsulation.*

the disease. Penicillin was given in 4 cases, chlortetracycline in 2, and oxytetracycline in 1, without influencing the course of the disease. These results are similar to the experimental findings of Strauss, Klingman and Pillsbury,[16] who performed studies in vitro and in vivo. They used chlortetracycline, oxytetracycline, penicillin, streptomycin, chloramphenicol, amithiozone, sulfoxone, para-aminosalicylic acid, N, N-bis hydrazine and sodium sulfadiazine. In vivo studies in mice demonstrated that sodium sulfadiazine gave 100 per cent protection against death from infection with *N. asteroides* when administered in doses of 50 to 100 mg. per kilogram of body weight daily. None of the other drugs approached it in efficacy.

In the administration of sulfadiazine the oral route may be used, and approximately 6 to 10 gm. daily should be given. Ideally, the blood concentration of this drug should be kept between 16 and 20 mg. per cubic centimeter. The duration of treatment depends to some extent on the severity of the disease and the response to medication. One should plan on several

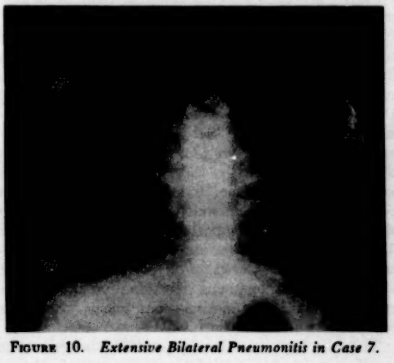

FIGURE 10. *Extensive Bilateral Pneumonitis in Case 7.*

weeks of treatment but may have to alter the dose or even discontinue use of the drug temporarily if renal complications arise. Urinalysis and determination of blood urea should be made frequently; the likelihood of impairment of renal function may be minimized by the concomitant administration of sodium bicarbonate.

One of the 3 patients who received sulfadiazine was treated for three months, and the other 2 for five months. The disease responded in each case. One patient recovered completely and is well seven years later. A second patient recovered from nocardiosis but died subsequently, presumably from Cushing's disease. The third patient died from an intracerebral abscess due to *N. asteroides,* but the pulmonary lesion disappeared roentgenologically during the administration of sulfadiazine.

Surgical treatment should be given as indicated. This includes drainage or excision of abscesses wherever they may occur. It may be superfluous to mention that adequate rest and nourishment are desirable.

Pathological Considerations

From the standpoint of gross pathology the lung was the most frequently involved organ. It was apparently the primary site of the infection in 6 of the 7 cases. The brain and the spleen were involved in 2 cases each, and in 1 of these the spleen appeared to be the source of generalized peritonitis caused by

N. asteroides. Grossly, most of the lesions took the form of abscesses, which were generally multiple and often confluent. The absence of extensive scarring, burrowing or sinus formation served to differentiate most of the lesions from those caused by *Actinomyces israeli.* From the gross appearance alone, the lesion was likely to be confused with suppurative processes due to common pyogenic organisms or caseous tuberculosis—that is, it was more characteristic of suppurative processes and tuberculosis than of actinomycosis.

The histologic reaction of various organs and tissues to infection with *N. asteroides* was remarkably uniform in the 5 cases studied at autopsy. Worthy of emphasis was the extensive necrosis of tissue with the formation of confluent abscesses and the absence of encapsulation (Fig. 9). In most cases there appeared to be little or no attempt at localization of the abscesses. Occasionally, there was a partial wall of loose granulation tissue, and rarely bands of fibrous tissue incompletely encircled the lesions. Daughter abscesses in the neighboring tissue were common. The absence of localization of the lesions, particularly those in the lungs, probably accounts for the widespread hematogenous dissemination in 3 of the cases. When dissemination does occur, the brain is especially likely to be involved.

The histologic reaction is quite distinct from the reaction to *A. israeli,* which usually calls forth extensive fibrosis, and in the abscesses the so-called sulfur granules are often found. Such granules were not observed in any of our cases. Worthy of emphasis also is the fact that the lesions did not resemble granulomas. Although necrosis of tissue was always observed, it was not associated with the formation of epithelioid cells, it was accompanied by minimal formation of granulation tissue, and only occasionally were giant cells observed. Fibrous encapsulation was not a feature of these lesions.

Finally, it is noteworthy that accurate diagnosis cannot be made by histologic examination. The organisms are not visible with hematoxylin and eosin stains and can be found only by the use of special stains such as the Brown–Gram technic. The organisms form gram-positive (granular), branching mycelia approximately 1 micron in diameter. Even this finding is not sufficient for a definitive diagnosis. For accurate diagnosis, identification of the organism by cultural methods is mandatory.

Bacteriologic Considerations

The cultural features of species of nocardia are well given in *Bergey's Manual*[11] and in modern textbooks of medical bacteriology. These micro-organisms grow as fine, branching filaments that may fragment into bacillary or coccoid forms. Some stains are acid fast and may be confused with tubercle bacilli. In Case 4 the organisms might easily have been so misinterpreted if bronchoscopy had been done. Although the filaments in histologic sections are seldom if ever visible with the usual hematoxylin and eosin stain, they are easily demonstrated by the technic described by Brown and Brenn[17] for applying the gram stain to tissues.

In the diagnosis of pulmonary nocardiosis, many problems may be encountered. Gastric washings, commonly used to make cultures for tubercle bacilli, may contain nocardia because of its wide distribution among food materials. An occasional colony may occur apparently as a contaminant on cultures made from specimens of sputum, but if numerous colonies are present on repeated examinations and if no other recognizable pathogen can be found, it may be justifiable to consider them as probably being causally related to the pulmonary lesions.

When the intrapulmonary lesions occur in small children and infants, it may be impossible to collect specimens of sputum. In such cases, if the intrapulmonary process has not responded to ordinary medical management within a week or two, it appears advisable to collect material from the trachea or bronchi by bronchoscopic means. In Case 7, smears of the trachea and bronchi taken at autopsy showed the organisms to be present in large numbers, so that culture of adequate material from these regions would probably have given the correct diagnosis.

In Cases 2, 4 and 5, the histologic features were such that one could hardly expect the organisms to be found in either sputum or bronchial secretions. In such cases it appears advisable to obtain a suitable specimen of lung for biopsy. In such a procedure it is suggested that several small lesions are more likely to contain the causative agent than one large lesion, since micro-organisms are seldom uniformly distributed in pathologic processes of this type. A generous sampling is also advocated because an adequate bacteriologic examination must include the inoculation of animals and the making of cultures for tubercle bacilli, various fungi and such bacteria as brucella, hemophilus, klebsiella and pasteurella. In addition, it may be necessary to examine the material for amebas and to make other tests, including chemical examination for such substances as beryllium, silicon and barium. The purpose of the biopsy is to determine as accurately as possible the cause of the condition, and the laboratory should be prepared to do whatever is necessary to establish the nature of the causative agent. For this purpose a generous specimen may be needed.

Summary and Conclusions

Seven cases of intrapulmonary nocardiosis are presented from the standpoint of clinical, roentgenologic, pathological and bacteriologic findings.

The lungs appeared to be the primary site of infection. In 3 cases metastatic lesions involved the brain.

In none of the cases did the disease respond to antibiotic therapy. However, in 3 cases in which it was recognized and treated with sulfonamides, the patient responded rapidly to this treatment.

There were no clinical, roentgenologic or laboratory data that would serve to distinguish intrapulmonary lesions due to *Nocardia asteroides* from those due to subacute or chronic infection with other common microbial agents.

Intensive efforts should be made to determine the etiologic basis of any intrapulmonary infection that fails to resolve on antibiotic therapy. The diagnosis of nocardiosis can be made only by isolation and identification of the organism from suitable clinical material. Such material may need to be obtained by bronchoscopy or even by biopsy of pulmonary tissue.

The pathologic process was dominated by necrosis with suppuration and the accumulation of a few macrophages. Fibrosis was minimal or nonexistent.

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UPTAKE OF AMMONIA BY MUSCLE*

Its Implications in Ammoniagenic Coma

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AN elevated blood anemia content has been reported to be a feature of hepatic coma by a number of laboratories,[1-4] but high levels have not always been found in this syndrome. Observations made during the course of an investigation of the cerebral uptake of ammonia[5,6] suggested that the finding of a normal venous ammonia level in hepatic coma might well be due to an uptake of ammonia by muscle. The following data show that this is indeed so, and that in the presence of a significantly increased arterial ammonia level the muscle can remove an amount of ammonia sufficient to convert a toxic arterial concentration to a normal, or nearly normal, venous level.

Method

Blood was drawn without stasis from the femoral artery and the femoral or antecubital vein into a previously calibrated 2-cc. syringe. The plunger was moved to the 2-cc. mark with the needle pointing upward to remove any bubbles of air that might have entered the syringe, and 1-cc. specimens were ejected into each of two Seligson microdiffusion vessels. The determination of ammonia was made as described previously.[6] In all cases a blank of water and two standard samples of ammonia nitrogen (one of 1 microgm. and one of 2 microgm.) were run with each pair of arterial and venous samples. The maximum range of colorimeter readings for the standard samples from day to day, with the blank as 0 in the Klett colorimeter, was 49 to 56 for the 1-microgm. and 98 to 110 for the 2-microgm. sample. For any run the maximum difference between twice the reading for 1 microgm. and the reading for 2 microgm. was 6 per cent of the reading for 2 microgm. The maximum difference between any pair of values for the blood samples reported was 10 per cent of the mean of the pair. The mean difference between pairs for one hundred consecutive determinations was 4.14 ± 2.71 per cent. The elapsed time between the entrance of blood into the syringe and the contact of the blood with the alkaline solution in the diffusion vessel was fifteen to forty-five seconds. Experiments to be reported show no alteration in values obtained over this period. The 14 patients studied were volunteers or comatose patients from the medical wards of the Maryland University Hospital. Where clinical evalua-

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tion of the depth of coma is reported the observation was made by at least 2 clinicians before the blood was drawn for the determination of ammonia concentration. Except as noted, none of the patients were receiving special therapy such as low-nitrogen diets, ammonium chloride, or amino acids.

Results

Figure 1 plots a series of 43 determinations of arterial and peripheral arteriovenous difference on 10

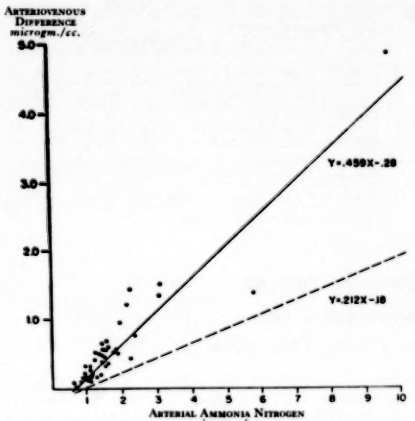

Figure 1. *Uptake of Ammonia by Resting Muscle As a Function of the Arterial Concentration.*

patients with and 4 without clinical evidence of liver disease. The 4 values below 1 microgm. of arterial ammonia per cubic centimeter are from the "normal" patients.

The arterial level of ammonia nitrogen in micrograms per cubic centimeter is plotted against the amount of ammonia removed by the muscle, the arterial minus the venous level. The dotted line is the regression curve for similar data on the arteriovenous difference across the brain taken from a previous report.[6] The uptake of ammonia by muscle is about twice as great as that by brain. There is much less scatter for the uptake of ammonia by muscle than there is for that by brain.[6] The correlation coefficient (Pearson's) for these data is 0.92.

Figure 2 depicts the arterial and venous ammonia levels in a patient with cirrhosis who had typical episodic coma, terminating fatally while she was under observation. The degree of coma is represented as vertical bars and is defined as follows: 1+ coma, lethargy with disorientation (the patient replied to questioning, but was unsure of the date or time or other essential details); 2+ coma, somewhat deeper lethargy or stupor, but the patient responded to questioning; 3+ coma, slight response to physical stimuli by grunts, with no response to questioning; and 4+ coma, the patient made no response even to the needle puncture for drawing blood. Two facts are of interest in this case. In the first place the venous ammonia was elevated only rarely, and at no time was it raised more than 25 per cent above maximum normal (1.0 microgm. per cubic centimeter by this method[6]). The second feature is the parallelism between the depth of coma and the arterial level of ammonia. The venous level also paralleled the coma, but since it was never greatly elevated, these variations could easily be interpreted as fluctuations in the normal range.

Case Report

A.M., a 55-year-old woman who was known to be alcoholic, was admitted to University Hospital on January 17, 1955, with a history of slowly increasing abdominal distention for about 2 weeks. During the 2d week she had received diuretics (mercurial and Diamox) and digitalis therapy. On this therapy there was no improvement in the ascites, and the patient became somnolent. On admission she was semistuporous and jaundiced, and had marked ascites without peripheral edema. The liver edge was 15 to 20 cm. below the right costal margin and was grossly irregular and nodular. Neurologic examination showed unequal pupils; only the smaller pupil reacted to light. The upper extremities had hyperactive deep tendon reflexes, and the lower were normal. The patient reacted to pain and was aroused with difficulty. At no time in her course was a "flapping tremor" elicited.

Examination of the blood revealed a hemoglobin of 12.1 gm. per 100 cc. and a white-cell count of 11,700,

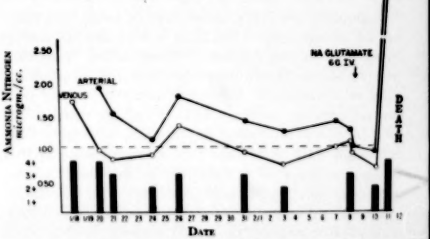

Figure 2. *Arterial and Peripheral Venous Levels of Ammonia in Relation to the Degree of Coma in a Woman with Cirrhosis.*

with a normal differential. The blood sugar was 101 mg., and the urea nitrogen 8 mg. per 100 cc.; the carbon dioxide content was 28 milliequiv., the sodium 123 milliequiv., and the potassium 4.4 milliequiv. per liter. The serum albumin was 2.5 gm., and the globulin 5.1 gm. per 100 cc. Thymol turbidity was 8.8 units; the bilirubin was 8.3 mg. per 100 cc. direct and 4.0 mg. total. A preparation for sickling was negative. The sedimentation rate was 36 mm. per minute corrected. The prothrombin content was 44 per cent of normal.

Abdominal paracentesis yielded 2 liters of yellow fluid, which gave a ++++ protein test (sulfosalicylic acid). Section of the sediment revealed no malignant cells. Blood and urine cultures were negative. The urine had a specific

gravity of 1.016, with a negative test for albumin, a trace of sugar, a negative test for acetone and a ++++ test for bilirubin, and the urobilinogen test was positive at a dilution of 1:60. A stool was positive for blood by the guaiac test.

Supportive therapy, with replacement of fluid and electrolytes and withholding of all nitrogenous intake, resulted in an improvement in the mental state and a concomitant drop in the blood ammonia nitrogen levels (Fig. 2). The blood urea nitrogen slowly rose and reached 256 mg. per 100 cc. 2 days before death. On February 8, 6 gm. of monosodium glutamate was given intravenously in 250 cc. of 5 per cent glucose. There was a fall in both arterial and venous ammonia that continued through the next day, with some improvement in the sensorium. On the following day the patient lapsed suddenly into deep coma, and the blood ammonia rose to the extreme levels shown in Figure 2. The blood pressure fell to unreadable levels, and was brought back to 100/80 with continuous administration of arterenol (Levophed), but the patient died about 18 hours later. Blood chemical studies in the 3 days before death revealed only a slight drop in carbon dioxide content to 17 milliequiv. per liter. The thymol turbidity had fallen to 3.8 units, and the van den Bergh test showed a direct bilirubin of 2.0 mg. and a total of 5.3 to 6.6 mg. per 100 cc. Autopsy was not performed and the final diagnosis was Laënnec's cirrhosis.

Comparison of Peripheral and Cerebral Uptake

Figure 3 is a plot of 17 simultaneous determinations of arterial, peripheral venous and jugular-bulb blood ammonia on 6 patients. The circles represent the cerebral, and the triangles the peripheral uptake of ammonia. The abscissas represent arterial blood ammonia, and both cerebral and peripheral points lie on the same vertical line. In only 2 cases was the cerebral uptake of ammonia greater than the peripheral uptake, and in 1 there was an evolution of ammonia from the brain. This occurred two hours after the oral administration of 7.5 gm. of asparagin. The regression lines obtained separately for peripheral and cerebral arteriovenous differences have been plotted. It must be noted that the scales for Figures 1 and 3 differ, since the highest arterial value in Figure 3 is about half the maximum value in Figure 1. In spite of considerable scatter the data cluster about the corresponding regression lines. The two relatively low values for the muscle uptake of ammonia in the patient with an arterial ammonia of about 5 microgm. per cubic centimeter possibly are explicable on the basis of the fact that he was moribund; we have noted such a drop in ammonia uptake a few hours before death in other cases. It is also noteworthy that measurements of peripheral venous ammonia together with jugular-bulb ammonia will give a spurious picture of the uptake of ammonia by brain. Figure 1 shows that the muscle removes approximately 40 per cent of the ammonia that reaches it whereas, as has been shown, the brain removes about 20 per cent. In Figure 3 it can be seen that for a particular case the brain usually removes less ammonia from the blood than the muscle removes. Comparison, therefore, of peripheral venous with cerebral venous ammonia levels will provide an apparent evolution of ammonia from brain equal to about 20 per cent of venous ammonia. As previously reported[5,6] the brain actually does take up ammonia when the arterial level is elevated, if this measurement is made as an *arterial*-cerebral venous difference.

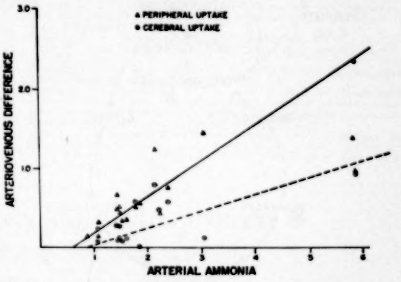

FIGURE 3. *Simultaneous Cerebral and Peripheral Uptake of Ammonia.*

Discussion

It has long been known, from the work of a number of investigators, that the amount of ammonia in the blood leaving the muscle of normal persons and animals at rest is approximately equal to the arterial ammonia, and that there is some increase in the ammonia content of venous blood after exercise.[7-10] A report by Strehler, Haas and Rupp[11] that arterial ammonia (capillary) is higher than venous has received little attention in the subsequent literature. All the experimental and clinical work on the metabolism of ammonia in hepatic disease appears to have been based on observations of venous blood levels of ammonia.

The consistent difference between arterial levels of ammonia and the corresponding peripheral venous levels makes it necessary critically to re-examine the data on the relation of blood ammonia levels to hepatic coma. It is obvious that the venous values do not reflect the concentration of ammonia in the arterial blood that enters the brain. In this connection the recent report of Havens and Child[12] on the relation of venous ammonia to psychotic symptoms might have shown even more of a parallel between severity of symptoms and ammonia concentration if arterial ammonia had been studied.

The observations of Riddell, Kopple and McDermott[13] on the syndrome of meat poisoning in the Eck-fistula dog suggest a causal relation between blood ammonia and clinical findings, but the data show only a rough parallel between the level of venous ammonia and the state of consciousness. Frequently, coma was present even in the face of a relatively low venous ammonia. The same absence of close correlation between the depth of coma and the venous ammonia concentration can be seen in the data of McDermott and Adams[2] and of Phillips and his associates.[3] Bess-

man and Evans,[14] on the other hand, found a definite correlation between arterial ammonia levels and cerebral depression in heart failure.

Since muscle has an active glutamic dehydrogenase, and since the Krebs cycle is the major oxidative pathway in muscle, it would be reasonable to infer that the same type of utilization of ammonia would occur in muscle as occurs in brain. This reaction, the synthesis by brain of glutamic acid from the alphaketoglutaric acid generated through the Krebs cycle, has been postulated as the mechanism of hepatic coma

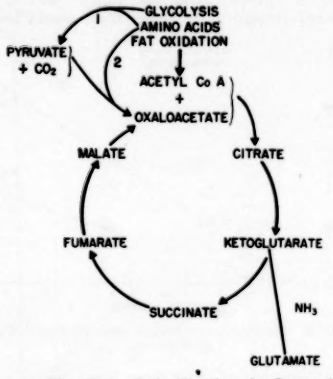

FIGURE 4. *The Krebs Cycle, Showing the Proposed Site of Action of Ammonia and Possible Pathways for Replenishment of Losses from the Cycle.*

A number of intermediate steps in the cycle have been omitted since they are not germane to the present discussion.

when the arterial ammonia concentration rises.[5,6] The pathogenesis of the depressed cerebral metabolism is based on the loss of alphaketoglutaric acid from the Krebs cycle in brain, resulting in the slowing down of this cycle (Fig. 4). If this is the basis of cerebral depression, should a similar lesion of the Krebs cycle in muscle not depress muscle activity? The clarification of this point is the key to the difference between the response of brain and muscle to Krebs-cycle lesions. Attention must be called to the various methods by which any losses of intermediates from the Krebs cycle might be replenished in brain and in muscle. Figure 4 shows the drain of alphaketoglutarate from the Krebs cycle when ammonia is being utilized to form glutamic acid, and the various reactions that might replace any intermediates of the cycle. Replacement of any intermediate would result in regeneration of the cycle, just as removal of any intermediate would result in inhibition of the cycle.

Figure 4 implies many possible pathways for the replacement of members of the Krebs cycle. For instance, blood-borne members of the cycle could replenish any losses that might occur. The active formation of all these intermediates by kidney could furnish a buffer for any losses. This utilization of blood-borne metabolites does occur in muscle, but, unfortunately, the brain is almost impermeable to acids, and no Krebs-cycle intermediates can enter brain as they can enter muscle.[15]

Another mode of replacing Krebs-cycle intermediates would be by oxidative deamination or transamination of aspartic acid to form oxaloacetic acid (pathway 2, Fig. 4). This mechanism, although available in brain, probably for formation of aspartic acid, can obtain no exogenous source of aspartic acid because of the impermeability of the brain to organic anions mentioned above. However, muscle can utilize this mechanism quite successfully.

A third method for buffering losses from the Krebs cycle could be by forming oxaloacetic acid (or malic acid[16]) by condensation of pyruvate, generated from glycolysis, with ubiquitous carbon dioxide. This process is called carbon dioxide fixation (pathway 1, Fig. 4). Interestingly enough, enzymes capable of performing this synthesis have been found in abundance only in liver and heart muscle. It is noteworthy that even when the skeletal muscle lacks a protective mechanism for the oxidative process it is still present in heart muscle. This extra defense against metabolic lesions possessed by the heart may help explain the extraordinary resistance of the heart to metabolic injury.

It is clear that the brain, the most restricted organ from the standpoint of metabolic substrate, is also the most limited in its defense mechanisms against biochemical insult to the Krebs cycle. This meager reserve capacity against loss of crucial intermediates may give a clue to the greater susceptibility of brain than any other organ to severe metabolic impairment by a great variety of toxic agents.

Studies of circulating substances metabolized by muscle have limited significance in interpretation of cerebral symptoms presumably due to these intermediates, if venous blood is sampled. The most that can be said for peripheral metabolic studies in brain physiology is that they represent the behavior of muscle in a particular mental state. It is recommended that studies of ammonia levels in relation to coma be done on arterial blood.

SUMMARY AND CONCLUSIONS

Data showing that the muscle removes approximately 40 per cent of the ammonia that arrives in the arterial blood are reported. It is shown that the muscle removes about twice as much ammonia from the blood as the brain does. The possibility that this uptake of ammonia by muscle masks a direct relation between blood ammonia and the symptomatology of ammoniagenic coma is advanced.

The biochenical basis for ammoniagenic coma is discussed, and the suggestion is made that a lesion of

the Krebs cycle in brain will be severer in its consequences than a similar lesion of the Krebs cycle in other organs, because the brain possesses comparatively few mechanisms for replenishing losses from the cycle. In this respect it is noted that heart muscle has perhaps the most varied protection for the cycle.

In view of the specific toxicity of ammonia and its relation to mental symptoms the more inclusive term ammoniagenic coma is suggested.

We are indebted to Dr. Theodore E. Woodward, chief of the Department of Medicine, University of Maryland Hospital, for his co-operation in obtaining the information reported in this paper and for his valuable advice in the preparation of the manuscript and to the medical staff of the hospital for generous assistance.

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THE RELATION OF MEGACOLON AND MEGALOURETER*

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BOSTON

In the course of caring for a number of patients before and after operation for Hirschsprung's disease it became evident that some had defects in bladder function. To eliminate this as a postoperative complication, studies of bladder function became routine preoperatively on patients of sufficient age for the performance of satisfactory cystometrograms. Fifty per cent were found to have a bladder capacity greater than normal and diminished or absent detrusor contractions. These changes persisted after correction of the megacolon. Five per cent of these patients exhibited more severe bladder dysfunction, with large quantities of residual urine and high intravesical pressure, and in these children there was dilatation of the upper urinary tract. Investigation of these patients with megaloureters ruled out mechanical obstruction at the bladder neck or at the ureterovesical junction.

Physiologic Description

The disturbed physiology of Hirschsprung's disease is the absence of peristaltic activity in the rectosigmoid colon. Absence of ganglion cells in the myenteric plexus has been related to the disturbed peristalsis. The ganglion cells in Auerbach's plexus are part of the parasympathetic nervous system. Since the lower colon is invariably affected in these cases, the fact that this area of colon receives its parasympathetic supply from the second, third and fourth sacral nerves suggests that congenital megacolon is a malformation in the pelvic parasympathetic system inhibiting the development of ganglion cells in the affected organ.

The pelvic parasympathetic system also normally supplies the urinary bladder; this is important in the understanding of patients with megalobladder associated with congenital megacolon. Detrusor function is thought to be dependent upon and co-ordinated to some extent by the pelvic parasympathetic nerves. We have demonstrated this relation with division of the pelvic nerves in 10 dogs in the laboratory.

The pelvic nerves are exposed extraperitoneally through bilateral inguinal incisions and divided near the bladder neck, with preservation of sympathetic nervous supply (Fig. 1). Control studies on each animal reveal a normal cystometrogram with strong sustained detrusor contractions after instillation of 100 to 200 cc. of liquid into the bladder. Immediately after operation all detrusor activity ceases—even with instillation of twice the initial amount of fluid (Fig. 2). This lack of detrusor activity had persisted in 6 animals examined three months after

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operation. Of course, complete division of the pelvic nerves cannot be assumed to be analogous to the anatomic situation in patients with megalobladder. Yet interruption of the parasympathetic nervous supply to this organ in the laboratory animal produces

FIGURE 1. *Diagram of Autonomic Supply to the Bladder, Showing the Site of Division of the Pelvic Nerves.*

changes in functions similar to those found in patients with this condition.

The underlying pathological anatomy in these cases of megalobladder with megaloureters has been examined. Since the lack of ganglion cells is characteristic of congenital megacolon, the distribution of ganglion cells was studied in relation to megalobladder. No absolute lack of ganglion cells from the bladder was found. In comparison with normal bladders, these large bladders had a relative diminution in the number and size of the ganglions, in the number and variety of nerve cells and in the number of nerve bundles. In 1 case a single nest of ganglion cells near one ureter was the only ganglion discovered throughout the wall of the entire bladder.

The association of two rare conditions such as Hirschsprung's disease and megaloureters requires postulation of a congenital defect in the parasympathetic system of such an extent that both colon and bladder functions are disturbed. If this concept proved to be valid, two other groups of patients would have to be postulated. The first would exhibit lesions limited to the portion of the parasympathetic system that supplies the colon. They would have a defect in colon function and a normal urinary bladder. We have observed a considerable number of such patients. In the second group the parasympathetic lesion would be limited to the portion of the pelvic autonomic system that supplies the bladder. We have treated 25 patients with normal colons and defects in bladder function identical to those observed in our patients with megacolon and megaloureters (Table 1).

DIAGNOSIS

Patients with a parasympathetic defect of the bladder can readily be identified by thorough urologic evaluation. The intravenous pyelogram demonstrates megalobladder with bilateral megaloureter. The urethra is normal as far as can be determined by the urethrogram after voiding and by endoscopic examination. The cystogram reveals a large, smooth bladder without trabeculations and inconstant ureteral reflux.

The cystometrogram is the most important examination in the identification of the aparasympathetic bladder; it must be taken before instrumentation has occurred. A continuous record of the bladder response to slow filling is obtained with the pressure-gauge and ink-writing apparatus. A slow drip of fluid is instilled into the bladder to hasten normal filling.

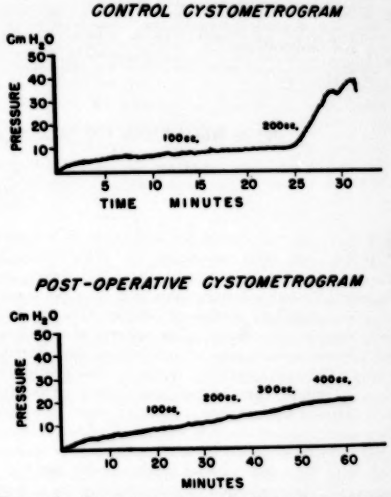

FIGURE 2. *Cystometrograms in the Dog before and after Division of the Pelvic Nerves.*

This is particularly important in patients with large bladders to permit completion of the test in three or four hours. These records are transcribed on slow-moving paper so that not only a constant record of the pressure but also the frequency, amplitude and wave form of all contractions is obtained. Normal cystometrograms in children usually record an initial pressure of near 0 and, before emptying, 12 to 15 cm. of water. There is usually no detrusor activity until the bladder capacity is reached, and then a series of contractions of increasing intensity occur. Patients with aparasympathetic bladders build up pressure to 30 cm. of water before the test is discontinued. Al-

though these children do not complain of fullness they become restless and make it impossible for the test to be continued. Occasional slow, low-amplitude contractions may be recorded, or there may be none at all. The forceful contractions noted in normal children are not recorded in these patients.

Studies of ureteral peristalsis demonstrate intact function of the ureters. At times there is slowing in the rate of peristalsis, but the amplitude is normal. It was determined by study of a group of patients with normal ureters that the average pressure developed by ureteral peristaltic waves was 35 cm. of water. It is quite obvious that these patients with intravesicular pressure of 30 to 35 cm. of water have a mechanical setup in which the ureter must work considerably harder than in the normal patient to transfer urine from the kidney to the bladder.

Treatment

On the basis of the hypothesis that bladder malfunction is the cause of dilatation of the upper urinary tract, a group of patients were placed on constant drainage either by suprapubic or by urethral catheter. There was a satisfactory improvement in the urinary-tract function as well as a decrease in the size of the ureters. It soon became evident that treatment of these patients by prolonged suprapubic drainage was cumbersome. The mechanical apparatus was difficult for the parents to manage. More recently bladder-neck resection was done in one group, the rationale being that opening of the bladder neck with micturition depends to some extent on the detrusor contractions, for some of the detrusor fibers are actually attached to the posterior urethra, and as these fibers shorten, the bladder neck opens; the patient with poor detrusor function has difficulty achieving an adequate opening of the bladder neck during voiding, and, consequently, the bladder neck actually serves as a partial mechanical obstruction. Resection transforms this area into an open fibrous channel so that resistance to voiding is reduced.

Table 1. *Causes of Megaloureter in 60 Patients.*

Cause	No. of Patients
Aparasympathetic bladder	30
Defect in ureteral peristalsis	15
Cord bladder	7
Mechanical obstruction	8

These patients are taught to use the bladder in the low range of pressure and to make a conscious effort to empty the bladder completely. They are placed on a program of voiding four times during the day and are awakened at night. Every effort is made to encourage them to empty the bladder completely with the assistance of the suprapubic manual pressure. Use of the bladder in the low range of pressure and elimination of residua accomplish a great deal for these children. We consider this method just as effective as suprapubic drainage, with obvious advantages for both child and parents.

The control of urinary-tract infection is an integral part of the treatment of these patients. Recent articles in the literature have not emphasized this fact sufficiently. Children with aparasympathetic bladders must be regarded as patients with chronic disease requiring long-term medical supervision. They are seen by their physician once a month as part of our program. At that time urinalysis is performed. If white cells are found in the sediment, the patient is catheterized to determine the residuum and to obtain a specimen for culture of bacteria and sensitivity studies. Thus, specific therapy is provided. Small doses of Gantrisin over long periods are necessary to keep some of these patients free from pyuria. In addition stronger wide-spectrum antibiotics are useful during exacerbations of bacterial infection.

Table 2. *Megaloureters Due to Mechanical Obstruction.*

Cause of Megaloureter	No. of Cases
Ureterocele	4
Posterior urethral valves	3
Anomaly of perineum	1

Discussion

It should be clear that our concept of the relation of megacolon and megaloureters is based on the fact that both conditions are related to a parasympathetic defect. It is a widespread idea that the relation of these two conditions is more simple. It has been suggested that megaloureters can be corrected by a resection of the distal ureter since resection of the distal colon corrects Hirschsprung's disease. There is no evidence that peristalsis is lacking in the distal portion of the ureter. Our studies have revealed that peristalsis is most vigorous in the distal portion. The operation that involves dissection in the region of the ureterovesical junction should be avoided if possible. The autonomic nerves enter the bladder in this region, and what little innervation these patients have may well be destroyed during dissection of the ureterovesical junction. We have seen 2 patients

Table 3. *Location of the Defect in Ureteral Peristalsis.*

Location of Defect		No. of Cases
Unilateral		11
Right	3	
Left	8	
Bilateral		4
Total		15

on whom resection of the distal ureter was performed. One child was unable to void postoperatively and became dependent on catheter drainage. The second had urinary residua that rose from 40 cc. before to 400 cc. after operation. For these reasons reimplantation of the ureter for reflux is also an unwise procedure in children with megaloureters caused by aparasympathetic bladder.

Other causes of megaloureter were found when all patients with this condition were analyzed. Mechanical obstruction such as posterior urethral valves or ureterocele caused only 10 per cent of the megaloureters in this analysis (Table 2). Relief of mechanical obstruction is achieved with standard methods. Another interesting group of patients with megaloureter on an entirely different basis was identified (Table 3). These patients, comprising almost a quarter of the series, had normal bladders but lacked peristalsis in one or both ureters. We have found patients with congenitally aperistaltic ureters most difficult to manage since the disease is progressive, with gradual destruction of all renal tissue. Control of infection is an extremely important feature of their care. There is hope that some other organ can be used to replace the defective ureter. Of the 60 patients with megaloureter, half were found to have the parasympathetic defect of the bladder. Congenital aganglionic megacolon was associated with a fifth of the defective bladders.

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PREDNISONE IN THE TREATMENT OF RHEUMATOID ARTHRITIS*

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PHILADELPHIA

THE new adrenocortical steroid prednisone[1] was used in the treatment of 33 patients with rheumatoid arthritis.

Prednisone and the related steroid prednisolone have been shown to possess a high degree of adrenocortical activity[2] and to be highly effective clinically as antirheumatic and inflammatory agents.[3-5] So far, in addition to rheumatoid arthritis and allied conditions, certain allergic disorders,[6] bronchial asthma[6-9] and pemphigus vulgaris[10] have been reported to respond. Bunim et al.,[11] studying the metabolic effects of prednisone and prednisolone, observed no retention of sodium or increased loss of potassium as a result of their administration. Although the drugs are three or four times more potent than cortisone and two or three times more potent than hydrocortisone, no proportionate increase has occurred in the frequency or severity of undesirable side effects.[3-11]

Material

Among 33 patients with rheumatoid arthritis treated with prednisone, the disease was of long duration in 23. In 9, it had existed between six and twelve months. In 1 the arthritis was acute.

The patients ranged in age from seventeen to seventy-five years. The duration of symptoms ranged from a few days to thirty years. There were 19 females and 14 males. At the time of initiation of therapy, 4 patients were known to be diabetic, 1 patient had an inactive asymptomatic duodenal ulcer, 2 patients had moderately severe hypertension, and 1 patient had far-advanced symptomatic ulcerative colitis.

Twenty-three patients had previously been treated with ACTH, cortisone, hydrocortisone, gold or phenylbutazone or combinations of these drugs. In each of these cases, it had been necessary to discontinue treatment because of unfavorable response or adverse reactions. Sixteen patients showed an early favorable response to cortisone but later escaped from control, and required larger and larger doses to obtain a lessened degree of relief. In 5 patients toxicity to gold developed. One patient manifested severe hypertension during cortisone and ACTH administration; in another, congestive heart failure and edema developed, and still another, with unrecognized diabetes mellitus, went into diabetic coma while receiving cortisone. The remaining 10 patients had had no previous specific therapy.

With the criteria of the American Rheumatism Association, the rheumatoid arthritis was classified as Stage 1 in 10 patients, Stage 2 in 16, Stage 3 in 5 and Stage 4 in 2. So far as functional impairment was concerned, none of the patients were in Class 1, 10 were in Class 2, 18 were in Class 3, and 5 were in Class 4.

Methods

The dosage of prednisone¶ by mouth on the first

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¶Kindly supplied as Meticorten tablets by George Babcock, Jr., M.D., Division of Clinical Research, Schering Corporation, Bloomfield, New Jersey.

day of therapy varied from 30 to 60 mg. Five patients received an initial dose of 20 or 35 mg. orally. The remainder of the first day's dosage and the other daily dosages were then divided, usually in equal parts, and given at intervals of six to eight hours. As the patients improved, the daily dosage was gradually reduced to a maintenance level, which varied from 12.5 to 30 mg. If symptoms recurred as the dosage was reduced, control could again be obtained by a return to the next higher dosage level. The duration of therapy varied from five to twenty weeks.

Results

All patients showed some degree of favorable response to prednisone. According to the criteria of the American Rheumatism Association, 17 patients had Grade 1 (complete), 15 Grade 2 (major improvement), and 1 Grade 3 remission (minor improvement).

Almost without exception, symptomatic relief began within four to eight hours of the initial dose. The first favorable sign was a striking reduction in pain and tenderness about the affected joints. By the end of twenty-four to forty-eight hours, stiffness, particularly early-morning stiffness, had lessened. Signs of inflammation about the joints tended to disappear about forty-eight hours after the initiation of therapy. Flexion contractures seemed to relax, the range of motion was increased, and the patients were able to perform acts such as feeding themselves, touching their chins, combing their hair and taking off rings, all of which had previously been impossible.

A rapid and significant drop in circulating eosinophils occurred four hours after an oral dose of 25 mg. of prednisone. The decreases in 6 patients so studied were 54, 74, 85, 85, 88 and 100 per cent, respectively. Erythrocyte sedimentation rates were promptly decreased during therapy in all but 1 patient.

Blood Pressure

No patient had an increase in blood pressure over the pretreatment level. One patient, previously hypertensive on cortisone, showed a gradual return to normotensive levels. Two other patients, normotensive before therapy, had a gradual rise in blood pressure during the first week of prednisone therapy and then slowly reverted to their previous normal levels. Both these patients had Grade 2 hypertensive retinal angiopathy, indicating earlier burnt-out hypertension.

Hemopoietic System

No consistent effects were noted in this system. The usual finding was a slight increase in hemoglobin concentration. A persistent leukocytosis (white-cell count of 10,000) was noted in 1 patient.

Gastrointestinal System

One patient, with a known active duodenal ulcer, showed no progression of his lesion when maintained on prednisone for thirty-five days. Two patients with inactive asymptomatic duodenal ulcer were started on prednisone. This fact was not known to us at the time. One of these patients complained of ulcer symptoms on the twenty-fifth day of treatment, when a gastrointestinal series disclosed a large ulcer niche. The other patient did not complain of ulcer symptoms during more than a hundred and twenty days' treatment with prednisone, but recent gastric x-ray studies have shown pylorospasm. One patient complained of mild epigastric distress, which was promptly relieved by antacids; no ulcer could be demonstrated. One patient had severe, far-advanced ulcerative colitis. On prednisone, bowel movements decreased from five or six a day to two a day, and the stools began to be formed.

Carbohydrate Metabolism

Four patients were known to be diabetic at the initiation of therapy. Three of them experienced an increase in hyperglycemia and glycosuria and now need additional insulin for control. The fourth patient has as yet demonstrated no increase in insulin requirements.

Electrolytes and Body Fluids

Studies of serum sodium and potassium in 6 patients revealed no hypernatremia or hypokalemia. Serum sodium levels, in the patients so studied, tended to decrease, rather than to increase, over the pretreatment levels. In 4 patients the decrease was less than 8 milliequiv. per liter; in 2 patients the level fell from 138 and 140 milliequiv. to 118 and 119 milliequiv., respectively. Serum potassium values remained constant at the pretreatment level in all patients studied. No patients complained of lassitude or muscular weakness, and no supplemental potassium salts were needed. Four patients showed a mild degree of facial rounding or "moonface." No patient gained a significant amount of weight on weekly weighings.

Acne and Hirsutism

Pronounced acne, which developed in 1 patient during cortisone therapy, did not regress during the administration of prednisone. Another patient had mild acne and hirsutism of the upper lip while on cortisone. Both conditions improved when cortisone was stopped but returned during prednisone administration, although to a lesser degree.

Mental Changes

The patient whose arthritis was of the longest duration, and who had the most severe functional impairment, demonstrated a sense of well-being that could only properly be called euphoria. No overt depressions or psychotic behaviorisms developed during the period of study.

Discussion

The two objectives of this study were to determine the effectiveness of prednisone in the treatment of rheumatoid arthritis and the type and extent of undesirable side effects.

The results, in general, agree with those of earlier published and unpublished reports. Prednisone has proved to be a valuable and potent addition to the accepted armamentarium for rheumatoid arthritis. It possesses antirheumatic and anti-inflammatory properties similar to those of cortisone. On a weight basis, prednisone appears to be three to four and one-tenth times as potent as cortisone.

More than two thirds of the patients in the present series could no longer be treated satisfactorily by conventional steroid therapy. Satisfactory remission for periods ranging from six to twenty-four weeks was obtained in all these patients with prednisone.

Objective and subjective improvement was noted in all cases within four to eight hours of the first dose. Relief from pain at rest and on motion occurred first, permitting a wider range of motion. Joint tenderness disappeared or became considerably reduced at about the same time. Inflammation about the joints, in the form of redness, swelling, heat, and effusion, tended to diminish beginning about the third day of treatment and had usually disappeared completely by the seventh day. There appeared to be no correlation between the grade or degree of symptomatic relief and the amount of structural damage in and about the joints.

The initial daily dosage of prednisone was 60 mg. in the first few patients. We were unable to find any advantage with this higher initial dosage, either in the speed of the remission or in its quality. Therefore, all subsequent patients in the series were started on a dosage of 30 mg. a day. The initial dosage was maintained for two or three days and then decreased by decrements of 5 mg. until the patient was maintained on 15 mg. per day. Any further decrements were by 2.5 mg. a day.

The optimal timing of the doses was determined by trial and error to be every eight hours. Clinic and private patients in the series took their medication on arising, in the midafternoon and at bedtime.

Excessive sodium retention alone or with excessive potassium excretion did not occur in any of the patients in this series. Indeed, patients taking prednisone for the longest periods (about twenty-four weeks) showed decreases in serum sodium, the greatest reduction being 22 milliequiv. per liter. This may be one of the chief advantages of this steroid — that is, that in the dosages necessary to maintain a satisfactory remission or amelioration of symptoms, sodium retention or potassium loss will not occur.

All patients were weighed at weekly intervals. None showed any excessive weight gain or peripheral edema, except 4 patients who had a mild degree of facial rounding. Several patients on concomitant therapy for congestive heart failure fully retained their cardiac compensation.

The existence of peptic ulcer may prove to be a relative contraindication to therapy with prednisone as it is with cortisone or ACTH. Of 2 patients with inactive duodenal ulcers at the time therapy was begun, a frank symptomatic ulcer developed in 1, and x-ray evidence of pylorospasm in the other. A third patient with a known duodenal ulcer when therapy was begun continued to show an ulcer niche despite four weeks of concomitant antiulcer therapy.

Summary

Thirty-three patients with severe rheumatoid arthritis were treated with prednisone, a new steroid with adrenocortical activity. The daily dosages ranged from 30 to 60 mg. initially to a daily maintenance dosage of 12.5 to 20 mg. A potency ratio of 3:1 or 4:1 as compared with cortisone was established. Objective improvement with a decrease in joint pain, tenderness and swelling and an increase in range of motion of affected joints occurred rapidly after the initiation of prednisone therapy. A significant decrease occurred in eosinophil counts and a moderate decrease in elevated erythrocyte sedimentation rates. Hypertension was augmented in 1 patient with essential hypertension, but hypertension in another caused by cortisone was relieved during prednisone administration. Prednisone had no adverse effects on blood sugar, serum sodium and potassium, or blood urea nitrogen levels. No patient had evidence of edema, and no glycosuria developed. One patient had a slight loss in body weight, 1 had a definite euphoria, and 4 had slight rounding of the face. A chronically scarred duodenal cap in 1 patient was adversely affected during five months' administration of prednisone by virtue of a pylorospasm.

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MEDICAL PROGRESS

PEDIATRIC VAGINITIS*

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PHILADELPHIA

THERE is a vast amount of literature and a comparable degree of interest concerning vaginal infections of adult women. Relatively little has been written about the same problems of children. Physicians tend to de-emphasize their significance and to treat them inadequately after an incomplete diagnosis. The average textbook of gynecology or pediatrics mentions the subject only briefly although two recent books[1,2] discuss it in detail. This review considers the common and some uncommon vulvovaginal infections occurring in the child up to the time of the menarche. It is written from the gynecologic point of view, with some notes of our personal opinions and experiences.

FUNDAMENTAL CONSIDERATIONS

It is important to realize that the genital anatomy of the female child is not merely a miniature of the adult. In contrast, the vulva of the child is situated more anteriorly; the introitus lacks the protection of hair and the padding of the mons and the labia, besides being in close proximity to the anal orifice. The labia minora are more conspicuous, and the clitoris is relatively large. Bartholin's glands and Skene's tubules are rudimentary. The hymen is quite prominent and becomes more so with straining. The vagina is of unusual length and of more upward direction than in the older woman. In the young child it is 7.6 to 11.4 cm. (3 to 4½ inches) long, or one ninth of the body length, in comparison with one fifteenth in the adult.[3] Its length increases only slightly during childhood. The thin walls are closely approximated and cryptiform, with a short posterior fornix. The ectocervix, or cervical portio, is similarly formed but is fairly regular, with few glands until the onset of puberty.[4] The well known reversal of the cervix-corpus ratio (1:2 in the adult and 2:1 in the child) is present; the corpus is naturally tiny, lying in a horizontal position. The tubes and ovaries are only slightly developed.

At birth both female and male infants are well endowed with maternal estrogens. These hormones are slowly excreted and destroyed after delivery. In the female a transient sexual precocity is noticed, the vulva being somewhat engorged, the hymen succulent and soft, and the vaginal epithelium about 20 to 40 cell layers in thickness.[5] Three layers (superficial or functional, intermediate, and deep or basal) are evident. The vaginal smear resembles that of an adult woman. The epithelium becomes only several layers thick in several weeks as hormonal support wanes. At first glycogen, deposited under the influence of estrogen,[6] is abundant, but this too diminishes to minimal amounts. At the time of puberty the epithelium once again becomes thicker and glycogen becomes evident.

Initially, the vagina is acid, with an average pH of 5.7,[7,8] and lactic acid is present.[9] On the fourth day of life, after the growth of Döderlein's bacilli, the pH averages 4.8 and remains so until about the ninth day, when the acidity gradually decreases so that by the third to sixth week the pH hovers near neutrality, often slightly on the alkaline side.[10] Here it remains during childhood until the time of puberty, when the vagina becomes more acid as ovarian function ensues.

At birth, too, the vagina is sterile, but in approximately twenty-four hours such organisms as staphylococci, enterococci and diphtheroids and others make their appearance.[11-13] A day later these are replaced by Döderlein's bacilli (lactobacilli) in practically pure culture. Whether these originate from fecal contamination is a moot question.[10] It has been shown, however, that their presence is maintained so long as there is sufficient estrogen in the circulation.[6] Within a week or ten days after this has been completely excreted the Döderlein bacilli are replaced by varied flora of cocci and diphtheroids.[13,14] The Döderlein bacilli are found in less than 20 per cent of children until puberty is attained.[15] There is some evidence also that the vaginal flora of the normal child is related to the flora of the upper respiratory tract.[8]

METHODS OF DIAGNOSIS

The history is derived from two sources: the parents or other adults caring for the child, and the child if she is at least five or six years old. The latter source should not be underestimated. The physician should inquire about the duration of the discharge, its character and any change in character. A history of bleeding leads one to suspect a foreign body or trauma. Note should be made of the acuteness of onset. The history of a possible contact with either infected children or adults is of significance. Associated complaints referable to skin diseases, urinary or rectal disorders and menstrual and systemic disturbances should be considered. Previous therapies — not only because they may alter the primary cause

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but also because their failure helps one plan more intelligent, subsequent treatment — should be catalogued as carefully and as accurately as possible.

Pelvic examination of the young child need not be the terrifying ordeal that has been pictured. With young children some sedation, occasionally anesthesia, may be necessary since it is dangerous to maneuver rigid instruments in a squirming child. With older children, a simple, honest explanation of what is planned — and why — may suffice. In a personal experience comprising over 80 cases in outpatient and private practice young patients have rarely been hospitalized for pelvic examination. Elaborate draping is not necessary. If the mother is overly solicitous only the nurse should be present. The instruments should be warm and out of sight. A "nonmedical" atmosphere should be encouraged. The parents should be made completely aware beforehand what is contemplated. It should be stressed that the child's "virginity" is in no way destroyed by a careful, thorough investigation.

The examination itself consists of three parts: inspection of the vulva; vaginoscopic examination, with the taking of necessary smears and cultures; and rectal examination. The child minds the last mentioned the least of all. For visualization of the vagina the inexpensive Kelly air cystoscope has been found the most valuable; an ordinary otoscope is not long enough and is ill shaped for this purpose although veterinary otoscopes may be used. Neither does a nasal speculum, commonly recommended, afford much view. In older girls, in whom even a small bivalve speculum produces discomfort by stretching, a proctoscope may be helpful. At times we have used the knee-chest rather than the lithotomy position since the vagina then "balloons out" with easier visualization. By means of the rectal examination, discharge can be "milked out" of the vagina. Bimanual examination (per rectum) in the very young discloses little except a tiny nubbin of cervix. In the prepubertal girl the uterine corpus is palpable. Gentle technic is essential even when anesthesia is used.

At some time during the course of therapy a vaginal inspection should be done, especially if the discharge is persistent, a foreign body is suspected, cervical disease is suspected or there has been a history of trauma. Allen[16-18] has pointed out the significant changes that may be missed in prepubertal girls when vaginoscopic examinations are not done, and it is likely that, with the growing interest in more examinations and less "cutting of corners" encouraged by various cancer groups, the premenarchal vagina will not be permanently neglected.

Laboratory studies on the vaginal secretions vary. Smears and cultures, including those for gonorrhea, should be routine procedures. These are easily obtained by the insertion of a catheter containing a drop of sterile saline solution.[1] Wet-smear examination determines the presence of red and white cells, the type of squamous cells and, in older girls, the presence of trichomonads and the hyphae and buds of candida. Papanicolaou smears, which should be taken with a dry applicator, help determine estrogen effect and possible malignant change. It has been the policy of the Vaginitis Clinic at the Jefferson Medical College Hospital to measure the blood sugar in all cases of mycotic infection. Needless to say, more elaborate studies are done as indicated.

Physiologic Causes of Leukorrhea

There are two occasions in the premenarchal girl when leukorrhea is to be expected and may be a normal finding: in the neonatal period and in the preadolescent period.

As mentioned above, the vulva and vagina of the newborn give evidence of considerable estrogenic activity. During the period when the Döderlein flora is at its height, a physiologic vaginal discharge, the "genital crisis,"[19] is quite common, being more noticeable in the full-term than in the premature infant.[20] In the older literature this was incorrectly considered an inflammatory process and misnamed "vulvovaginitis desquamativa."[21] There may be sufficient discharge to alarm the parents or physician, but smears rarely show anything but mature epithelial cells and the Döderlein bacilli. Direct inspection shows a thick, white mucoid discharge covering uninflamed and well epithelized vaginal walls. The thick vaginal epithelium and low pH apparently militate against vaginal infections, which are rare at this time. On occasion a blood-tinged or frankly bloody discharge occurs a few days after delivery and is analogous to pseudomenstruation which Cruickshank and Sharman[11] found to occur in 5 per cent of more than 900 female newborn infants.

Development of the genital organs toward the adult state begins four or five years before the menarche. The labia majora enlarge, pubic hair appears, and there is evidence of secretory activity in the Bartholin glands. Once again the vaginal epithelial wall thickens, glycogen is deposited, and acidity increases, all from estrogenic stimulation. Pre-existing vaginal infections may disappear. At this time a noninfective, hyperestrogenic adolescent leukorrhea[2] is often noted. This is presumably the result of excessive estrogenic production without the "balancing" effect of progesterone.[2,22] The discharge is white, milky and odorless; itching is infrequent. There may be some congestion of the external genitalia, but the vagina appears normal. Smears show good estrogen effect and many Döderlein bacilli, with few leukocytes. The pH is within normal limits.

In most cases, careful examination, explanation and reassurance are all that are required for treatment. Local hygiene and general systemic measures are helpful. Douches are rarely necessary. Progesterone or testosterone in small doses may be used to correct the underlying endocrine imbalance but is best avoided in this age group.

During adolescence also the cervical glands secrete more mucus, especially in cases of so-called "congenital cervical erosion" in which endocervical columnar epithelium is found ectopically on the portio beyond the external cervical os. Here, again, treatment may be postponed, if one is certain that the "erosion" is not carcinoma. In severe cases, biopsy and light cauterization are indicated.

Gonococcal Vaginitis

Gonorrheal vulvovaginitis is a highly contagious, but relatively rare, disease at present. Infection results from direct or indirect contact with the discharge of an infected person, usually an adult. In institutions, when proper precautions are not taken, the disease may spread from child to child. The infection is stated to be transmitted from linens, towels, bath tubs and thermometers. Toilet seats are probably of little significance in this respect.[23] Cohn, Steer and Adler[23] believe that intermediary objects play a minor part in transmission and that some form of sexual contact is the usual source of the disease. It is certain that the gonococcus is a fastidious organism with highly specific growth requirements. This is important to realize in medicolegal actions concerning gonococcal vulvovaginitis. The psychic trauma to the parents, some of which is necessarily reflected in the attitude toward the child, may assume alarming proportions, with the little girl made to feel unclean and unwanted. Both the English and foreign literature on gonorrheal vulvovaginitis is very extensive.

The primary sites of involvement are the vulva, vagina and cervical portio. Whether the endocervix is involved is still a question especially since the endocervix is rudimentary in development until about ten years of age. Santalow and Nowatelnowa,[24] after examining 9 post-mortem specimens, believe that it is not involved. A similar situation exists with the urethra; it is bathed in purulent exudate as part of the general inflammatory process but not primarily infected.[1] There is similar controversy regarding rectal involvement,[25,26] diagnosis based on culture giving a much higher incidence[26,27] than is ever suspected clinically. In the autopsy study cited above, 3 of 6 cases showed pathologic rectal changes. Inflammation of Bartholin's glands, arthritis and conjunctivitis are uncommon.[26] Dobszay has demonstrated the nonpatency of the genital tract during childhood, and probably for this reason pelvic peritonitis rarely occurs.[28] Vulvovaginal infection of the newborn[29] is met infrequently even if the mother has fullblown gonorrhea. This may be explained by the hypertrophy of the epithelium and the low vaginal pH at that time.

In mild cases, the vaginal mucosa, urethral meatus and vulva proper are reddened, with a thick, creamy, yellow discharge. The more severe cases may be accompanied by edema and much pain. Pruritus varies in intensity and may be accompanied by excoriation from scratching and masturbation. Systemic manifestations are characteristically minimal. As the disease becomes chronic the infection tends to become localized to the vagina with periods of remission. Vaginal adhesions may form.

All purulent vaginal discharges are suspect until several cultures have proved negative. Culture is the *sine qua non* of diagnosis especially since other gram-negative intracellular diplococci may be found on smear.[30,31] This is especially true for children receiving estrogen therapy, when it may be difficult to identify the organism in the smears.[26] If secretions for study are not readily available one can "milk out" the vagina by rectum as mentioned above.

Treatment

As with other forms of vaginitis in children, local hygienic measures should be carried out. Hospitalization or bed rest is rarely necessary. With gonorrheal infection special precautions must be taken. Until the child is cured she should not be permitted contact with other children, nor should she attend school. She should not sleep with other little girls, and her clothing and bed linens should be laundered separately. Individual toilet facilities are recommended; otherwise, the toilet seat should be kept scrupulously clean. Local manipulation, including rectal examinations, should be kept at a minimum. The disease should be reported to local health organizations according to the law. Criteria of cure are not nearly so much discussed as formerly. The routine is to take weekly cultures for several weeks and then two monthly ones.

The specific treatment of gonorrhea has gone through various stages, and it should be stated that even without therapy the infection tends to clear of itself.[32] Originally, treatment centered about the local instillation of antiseptics. These penetrated poorly, were difficult to administer and required a long time to accomplish their purpose. Silver, in the form of picrate suppositories, was used in the past.[33] More than twenty years ago, Lewis[34] demonstrated that estrogenic hormones are of value. His work was based on the facts that the infection was known to subside when the changes of puberty converted the delicate thin-layered epithelium of the child to the thicker structure of the adult, that estrogens were known to build up the vaginal epithelium of immature monkeys[35] and that the threshold of uterine bleeding is well above the level required to produce changes in the vaginal epithelium.[36] It should also be stated that estrogen lowers the pH of the vagina and increases hyperemia. The literature on the use of estrogens in gonococcal vaginitis has been well surveyed in an excellent review by Weed and Collins.[37]

Estrogenic hormones may be given locally in the form of vaginal suppositories or cream, by injection

or by mouth. There are certain objections to systemic administration[38] — namely, the temporary development of secondary sexual characters such as breast enlargement, vulvar engorgement and uterine hypertrophy with occasional anovulatory bleeding. Whether the estrogen has any harmful effects on normal development is unknown. Local application may not be feasible in some children. In children over four years of age, suppositories of 2000 international units (I.U.) or 0.1 mg. of diethylstilbestrol may be used nightly for four to six weeks; parenterally, 5000 I.U. initially, followed by 2000 I.U. every other day for two weeks and then by 2000 I.U. for about six weeks more is sufficient.[2] Oral administration of stilbestrol, 0.1 mg. with meals for a week and slow decrease of the dose over several more weeks, also provides adequate therapy.

After the introduction and extensive use of the sulfonamide drugs in the treatment of gonorrhea, treatment failures were encountered from the increased tolerance of various strains.[39] At one time, sulfathiazole and sulfadiazine were widely used.[40] These are given on the basis of 0.06 gm. (1 gr.) per pound of body weight per day at six-hour intervals, with increased fluid intake, for approximately a week. The course of therapy may be repeated. Results are better than those with estrogen alone.[32]

As of this date, penicillin is the mainstay of treatment. The treatment time is fairly brief, there are few side reactions, and the drug is very effective. It may be administered systemically, orally or by suppository.[41] Massive single doses have been tried.[42,43] With doses of 10,000 units per pound of body weight per day, smear and culture become negative in several days. The broad-spectrum antibiotics, in doses of 8 to 10 mg. per pound of body weight per day in four divided doses, can be given, but penicillin seems to be most efficacious.[39] Combinations of penicillin with estrogen[44] and of sulfonamides with estrogen[45] have been advocated. It seems that penicillin should be used primarily in all cases and the other drugs reserved for resistant ones.

Nonspecific Vaginitis

Nonspecific vaginitis refers to cases of vaginitis with leukorrhea in which a mixed bacterial flora but no specific micro-organisms are found; in the minds of some the term means "nongonorrheal." In many cases more careful and detailed cultural methods would yield a predominant organism or organisms. The precipitating causes may be trauma, masturbation, tight clothing, uncleanliness, systemic disease or even foreign body. The frequency of nonspecific as compared to gonorrheal vulvovaginitis is disputed, apparently depending on the social level of the children studied and the diagnostic methods employed. In the experience in the Vaginitis Clinic at the Jefferson Medical College Hospital, only 3 of 62 cases of vulvovaginitis in children have been gonorrheal. The remainder have all been nonspecific except for 1 case due to a foreign body. Nonspecific vaginitis is not contagious.

The bacteria cultured in such cases vary greatly. Reichert et al.[46] found that diphtheroids, *Staphylococcus albus, Streptococcus indifferens,* varieties of streptococci and hemophilus organisms predominated. Anderson, Schultz and Stein[47] report similar findings. Many authors have stressed the relation of nonspecific vaginitis to infections of the upper respiratory tract.[3,46,48] Weaver[31] has emphasized the value of cultures as compared with smears since *Neisseria sicca* can be confused with *N. gonorrhoeae* by the latter method.

As with gonorrheal vaginitis there is difference of opinion about the exact location of the inflammatory process in the lower genital tract. In early cases there is often urethral involvement, and though this may be temporary, the urethritis may not clear until the vulvovaginitis is effectively managed.[49] The vagina and cervical portio may show minimal inflammatory change, but vaginal ulceration and later adhesions and synechiae may form. Inflammation of Bartholin's glands, proctitis, inguinal adenitis and ascending infection are rare.

Clinically, the child complains of soreness and itching and the mother notices evidence of local inflammation and discharge on the underclothing. Urinary symptoms, such as burning, frequency and dysuria, may be present. Recognition of the condition depends on careful diagnostic measures, including a search for a foreign body.

Treatment is similar to that of gonococcal vulvovaginitis. Rest and a nutritious diet are important, as is careful local cleansing. The child should be taught to wipe anteroposteriorly after stool. If a specific micro-organism has been isolated, this should be treated by the appropriate antibiotic. Sulfonamides by mouth, instillation of antiseptic solutions and varous ointments, creams and suppositories have been utilized. Sometimes, merely putting a quantity of a buffered sulfa cream at the introitus several times daily is sufficient. Estrogen can be applied as in gonorrhea or may be administered in the form of miniature suppositories if the child is co-operative. Adult nitrofurazone urethral suppositories (Furacin) have also been used, with good results in 5 cases.

Nongonococcal Vaginitis of Specific Bacterial and Viral Origin

Diphtheritic

Laughton[50] isolated 34 strains of corynebacteria from the vagina, some strains being closely similar to *Corynebacterium diphtheriae.* With the noticeable decrease in the incidence of diphtheria, true diphtheritic vaginitis is seen much less than previously. Rosa and Tronelli[51] believe that the genitals consti-

tute a more favorable habitat than the throat for *C. diphtheriae* and *C. xerosis*. The vaginal infection may be primary or secondary; the secondary form may be associated with a throat infection, contact infection of a wound or even with infected urine.[52] Reviews of the early literature on this subject are available.[53-56]

Clinically, one notices diphtheritic lesions on the labia involving the vagina. There is ulceration, with characteristic membrane formation. The diphtheria bacillus may be isolated from the vaginal discharge. Systemic manifestations may be severe. Locally, gangrene (noma) may be found. Potter[29] describes a child, delivered of a mother with faucial diphtheria, who acquired primary vaginal diphtheria that resulted in death. Facial paralysis[57] and local atresia[58] from vaginal diphtheria have been recorded in the literature. Treatment consists of isolation and the appropriate antibiotics. It is interesting that antitoxin therapy was only moderately successful with vaginal diphtheria[59] in 1 case reported.

Pneumococcal

Pneumococcal vulvovaginitis in children has been reported on a few occasions. These organisms are reputedly destroyed by the normally acid vaginal discharge of the adult,[60] and although the infection would thereby be expected to be more prone to occur in children, Hardy[8] found pneumococci in only 1 of 343 examined. Boisvert and Walcher,[61] in a study of 524 vaginal cultures of 286 patients, found 11 with pneumococci. The presence of pneumococci in vaginal swabs may be of diagnostic value in suspected pneumococcal peritonitis.[62] Bickers[63] reported a case of vaginitis due to Type 2 pneumococcus in a nine-year-old girl after an upper respiratory infection; cure was effected by local instillation of Type 2 antiserum. Antibiotic therapy would be indicated at present.

Streptococcal

Streptococcal vulvovaginitis may occur during the course of, after or even without relation to scarlet fever.[64] Hedlund[65] found vulvovaginitis caused by hemolytic streptococci in 105 of 758 patients with scarlet fever; most of the cases occurred before the age of twelve. There is undoubtedly close correlation between strains in the vagina and throat since when grouping and typing of streptococci from both vagina and nasopharynx of the infected child are done, the same group and same type are found in each.[66]

Shigella

McGinness and Telling[67] have reported a case of vulvovaginitis in a seven-year-old girl that was due to *Shigella flexneri* identified by culture. Sulfaguanidine was given orally and locally by vaginal insufflation, with satisfactory results.

Viral

It is not unexpected that the viral diseases of childhood with skin manifestations — for example, varicella, measles and smallpox — may involve the lower genital tract.[68] With measles, diffuse vulvitis with an increase in vaginal discharge may be a prodromal stage. Schachter[69] has reported a case with abscess formation in a two-week-old girl. Vulvovaginal vaccinia in young children has been reported[70,71]; in 1 case the child was thought to have contracted the disease from a recently vaccinated sibling. Even primary herpetic (aphthous) vulvovaginitis occurs.[72,73] Local genital ulceration from which Coxsackie virus was isolated has been reported.[74] The lesions of molluscum contagiosum may also be found in the immature vagina.[75] Unexplained cytoplasmic inclusion bodies, probably of viral origin, have been described in the vaginal smears of young children with discharge.[76]

Foreign Bodies

Foreign bodies are not a frequent cause of leukorrhea in children. Schauffler,[77] in a series of 266 cases of vaginal discharge in children, found foreign bodies in only 4 (1.5 per cent). Nevertheless, they must be thought of and searched for.

Foreign bodies are not necessarily found in the vagina of "the naughty girl."[78,79] They are usually inserted out of curiosity in manipulation of a natural orifice by the child herself or other children in play. In exceptional cases they are introduced by criminal acts of adults. The various objects discovered are legion[80,81] — shells, hairpins, straight pins, safety pins, nuts, corks, paper crystals, cherries, plum pits, a powder box and even a leech. Sand may be present in the vaginas of female children who play on the beach for long periods.[82] The presence of the foreign body is often complicated by a nonspecific infection or even by a specific infection as gonorrhea[83] or Vincent's infection.[84,85] Bristowe[86] reported a vaginal calculus the size of a walnut in a paraplegic ten-year-old girl. The calculus was probably caused by constant trickle of urine into a relatively immobile vagina.

The clinical picture depends not only on the size and shape of the foreign body but also on its chemical constitution. The main symptoms are vulvovaginitis with leukorrhea that is characteristically blood tinged. A severe inflammatory reaction is noted locally, perhaps with ulceration. Scar tissue may form, as may fistulas. The diagnosis of a foreign body in the vagina is first made when one suspects its presence. Schauffler[1] recommends gentle probing of the vagina with a finger in the rectum. A click is heard if the object is metallic. Occasionally, the foreign body can be detected by a finger in the rectum alone, and if it is radiopaque it can be discerned on x-ray examination. Some form of vaginoscopic examination is ultimately essential. Treatment centers about removal of the

foreign body and management of the associated vulvovaginitis by the accepted means of therapy.

Helminthic Vaginitis

There are three worms that occasionally cause vulvovaginitis in children: the pinworm (also called threadworm, seatworm, *Enterobius vermicularis* and *Oxyuris vermicularis*), the roundworm (*Ascaris lumbricoides*), and the whipworm (*Trichuris trichiura*).

The female pinworm, having been ingested as an egg, grows, migrates to the perianal area (less frequently to the vagina), discharges its own eggs and dies. In the adult woman the worms may continue their migration up into the uterus and fallopian tubes.[87] The symptoms are attributed to mechanical stimulation, irritation, allergic reactions and passive transportation of pathogenic bacteria. Itching, vulvitis from scratching and moderate discharge are seen. The best routine method of diagnosis is by means of a scotch-tape swab made by application of scotch tape over a tongue depressor. This is firmly pressed against the perianal area early each morning. At times the female worms may be discovered in the anal area soon after the child has been put to bed. Treatment is aimed at eliminating this infestation from the intestinal tract in addition to careful local hygiene. Oxytetracycline has been advocated as effective in pinworm infestations,[88,89] but more time will be needed to assess its true worth.

Unlike the pinworm, the roundworm and whipworm do not directly invade the genital tract, the vulvovaginitis associated with these intestinal parasites being part of the general allergic and toxic manifestations to which the infestations give rise.[2] Here, again, treatment is directed toward elimination of the worms combined with management of the secondary bacterial infection of the vulvovaginal area.

Vaginitis Due to *Trichomonas Vaginalis*

Trichomonas vaginalis is unusual in the newborn, in prepubertal girls and in older women. Although it is most commonly found during the period of sexual activity, the possibility of trichomoniasis cannot be ignored in any patient merely because of age.[90] The apparent resistance of children is probably associated with the different physiology of the immature vagina, perhaps the lack of glycogen or even the elevated pH. It is quite likely that more infestations in children would be detected by cultural methods than by the wet smear.

Sporadic case reports have appeared in the literature. The disease has occasionally been discovered in the newborn infant.[91,92] In an effort to determine if female babies might be infected from mothers during birth, Trussell and Wilson[93] examined 41 babies of infected mothers within the first eight days of life; 2 babies (4.8 per cent) were found to be infected on the second wet-smear examination. Trussell[90] suggested that the infection might exist in children in a latent form for many years. Two children in the second month of life were thought to be directly infected by mothers who had trichomonal vaginitis.[93,94] Karnaky[95] reports a vaginal trichomonal infection in a ten-month-old child. Until just before the menarche or immediately afterward, the disease is said to be rare.[96-98] This has also been the experience here.

The clinical manifestations resemble those of the adult: purulent discharge, itching, local soreness and irritation being prominent. Treatment is hindered by the poor drainage, the difficulty of intensive local therapy and the lack of a specific trichomonacide. In several cases in premenarchal girls, combined oxytetracycline and polymyxin vaginal tablets or Floraquin tablets have been given in daily doses for ten to fourteen days. The tablets may be broken in half before use; they are more easily inserted after moistening with water. Water-miscible jellies, such as Nylmerate Jelly, may also be helpful. The physician should take time to plan his course of therapy and should be certain that the drug is inserted correctly.

Candidal Vulvovaginitis

Vulvovaginal mycotic infections from *Candida albicans* are rarely found in children, but they seem to be increasing in frequency as a result of the introduction of broad-spectrum antibiotics. Oral thrush may become disseminated in the newborn and may involve the genital area, especially if the child is debilitated.[99,100] It is somewhat surprising that vaginal thrush does not occur more often at this age since the vaginal secretion is acid and the epithelium contains glycogen, but possibly these factors are not "optimum" enough.[2] Here, again, cultural methods, such as Nickerson's medium,[101] could be used to advantage in the study of this problem.

In the 3 cases seen in girls in the Vaginitis Clinic of the Jefferson Medical College Hospital, all patients were between ten and thirteen years of age. Two, who were the daughters of women with diabetes mellitus, showed decreased glucose tolerance curves, and 1 had received large doses of a broad-spectrum antibiotic.

Treatment, besides withdrawal of the antibiotics, follows that used in adults, consisting of gentian violet and fatty acid preparations. Mention should be made of the fact that pregnancy should be considered in older girls especially if the vagina is widely patent.

Venereal, Granulomatous and Miscellaneous Lesions

As the child becomes older and nears the menarche, the opportunity for sex play becomes greater, and vaginal lesions of a venereal nature may be acquired. Granuloma venereum has been reported in preadolescents.[102] Lymphogranuloma venereum has even oc-

curred in early childhood[103] and with rectal stricture.[104,105] Tuberculous lesions of the vagina are met infrequently, but Wharton[106] was able to collect 10 cases in children ten years of age or under.

In addition to contact dermatitis of the vulvovaginal area, vulvovaginal pruritus on an allergic basis has been mentioned as a major symptom of ragweed pollinosis in young girls.[107] The external genitalia are reddened, but skin changes are minimal.

An unusual case of hydrorrhea vaginalis (dysfunctional, serofibrinous or allergic vaginitis) is reported by Franken and Rotter[108]; a twelve-year-old girl had a pseudomembranous vaginitis with a profuse serous discharge thought to exude directly from the vaginal wall; 8 per cent of the cells in the discharge were eosinophils. Subsidence of leukorrhea and local inflammation followed the use of local estrogen suppositories. Scheffey, Rakoff and Lang[109] described a similar case in an adult treated with local application of hydrocortisone.[109]

Purpuric disorders, leukemia[110] and agranulocytic diseases may affect the vagina as part of their mucosal manifestations. Ectopic ureters draining vaginally are sometimes seen. Nor should local genital cancer be forgotten in spite of its infrequency.

Summary and Conclusions

The anatomic and physiologic features of the premenarchal vagina, as well as methods of examination and diagnosis in the child with vaginal inflammation are reviewed. The most prevalent form of vaginitis in children is the so-called nonspecific variety, but specific agents, especially the gonococcus, must always be sought for. Cultural methods are universally preferable to smear. A plea is made for more thorough study of the child with a vaginal infection so that more specific therapy may be administered.

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Correction: In the paper entitled "Blood Levels from Orally Administered Penicillins G and V" by Jones and Finland, which appeared in the November 3 issue of the *Journal*, on page 754, in the last line, "−5°C." should read "+5°C." and at the end of Table 1 on page 758, under "Minimum Detectable Concentration in Plasma" "0.090" should read "0.0090" and "0.063" should read "0.0063."

MEDICAL INTELLIGENCE

DYSPHAGIA DUE TO HYPERTROPHY OF THE CRICOPHARYNGEUS MUSCLE OR HYPOPHARYNGEAL BAR*

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BOSTON

ACCORDING to Templeton and Kredel,[1] "The cricopharyngeus muscle is a true sphincter which can be easily demonstrated at Roentgenologic examination. When the Valsalva test is performed, the contraction of the cricopharyngeus is intensified."

Brunner[2] gives the following description:

> The purpose of the tonic contraction of the cricopharyngeal sphincter is to prevent oesophageal respiration and to ensure that sufficient air enters the lungs. A relaxation of the cricopharyngeal sphincter would cause the air to be sucked more readily into the oesophagus than into the lungs . . . the mound at the posterior wall of the hypopharynx may be called the "hypopharyngeal bar," and it should be realized that the finding of a hypopharyngeal bar indicates a spastic contraction of the cricopharyngeal muscle . . . the hypopharyngeal bar is caused by the increased air pressure in the hypopharynx.

In another article Brunner[3] carries his description further:

> In functional disorders of the pharynx there is frequently hyperexcitability of the cricopharyngeal muscle associated with moderate and periodical dysphagia. In approximately 50% of the cases there is retention of barium. Barium retention, though not of excessive degree, may occur in patients who do not show signs of a malignant lesion in a period of several years. The transitory hypopharyngeal bar is due to spastic contraction of the cricopharyngeal muscle, while the spontaneous, or permanent, hypopharyngeal bar is caused by permanent spasm of the cricopharyngeal muscle. A spontaneous hypopharyngeal bar is frequently noticed in diseases of the pharynx or close to the pharynx. It is associated with a retention of barium and is usually associated with dysphagia.

The object of the present paper is to report 2 cases of severe dysphagia in which nothing could be demonstrated by x-ray study or esophagoscopy except what we have described as hypertrophy of the cricopharyngeus muscle.

CASE REPORTS

CASE 1. H.S.D. (P.H. 195029), a 75-year-old man, first entered the hospital as a private patient of Dr. Richard H. Sweet complaining of difficulty in swallowing of 3 years' duration. One year before admission he became progressively unable to swallow solid foods until they were well chewed to a liquid state. He had difficulty even in swallowing liquids and basically in performing the act of deglutition. He regurgitated food and fluid through the nose. He had lost 9.1 kg. (20 pounds) in weight. There was also progressive hoarseness of 1 year's duration.

Physical examination was negative.

X-ray examination of the esophagus was reported as follows:

> The pyriform sinuses and vallecula epiglottica are widely distended, probably because of incomplete but chronic obstruction in the cervical esophagus. A great amount of barium spilled into the respiratory tree. There seemed to be no true paralysis. The narrowing of the cervical esophagus is smooth. It seems to be due more to extrinsic pressure than to intrinsic ulcerative tumor. The postcricoid space is somewhat wider than usual. There is a tiny spicule of barium projecting from the esophagus, such as is seen after a diverticulum has been removed. The findings suggest involvement of the cervical esophagus by some extrinsic mass.

Esophagoscopy was not done, but with a diagnosis of hypertrophy of the cricopharyngeus muscle Dr. Sweet incised the cricopharyngeus muscle. At the time of operation it was observed that the cricopharyngeus muscle was very thick and fibrous. It was incised in the midline posteriorly. Two pieces of the muscle edge were taken for biopsy purposes. Along the inferior margin of the muscle band there was a tight ring that felt very much like scar tissue. The pathological report was atrophy, fibrosis and chronic inflammation of the muscle. Postoperatively, there was no improvement in swallowing, and 2 weeks later a modified Stamm gastrostomy was carried out for feeding.

The neurologist carefully ruled out paralytic causes for dysphagia and also excluded myasthenia gravis. A year and a half later the question of gastritis was raised as a possible etiologic factor, but this was excluded by gastroscopy with biopsy. The patient remained on gastrostomy feedings for the rest of his life, dying of bronchopneumonia approximately 4 years after the gastrostomy.

At autopsy the pharynx was normal. The entire length of the esophagus had a smooth mucosa and a thin, pliable wall. There was no evidence of stenosis, ulceration or other gross disease of the esophagus. Microscopical examination of the esophagus showed numerous superficial ulcerations where the epidermis was lost and replaced by granulation tissue with acute inflammatory-cell infiltrate. Numerous lymphocytes, dilated small blood vessels and a few polymorphonuclear leukocytes were present in the subepidermal tissue. The muscles of the esophageal wall were considerably disrupted with fibrous scar in which a few muscle fasciculi were still present. The pathological report was: "histopathological changes consisting of focal degeneration of muscle with replacement fibrosis of the muscles of the upper esophagus." In summary the autopsy findings were neuromuscular degeneration of the esophagus, type undetermined, with chronic esophageal obstruction, bilateral bronchopneumonia of the lower lobe, probably due to aspiration, pulmonary emphysema, chronic heart disease involving the aortic and mitral valves, benign prostatic hyperplasia and fibrous peritoneal adhesions.

Nothing was ever found in this case to explain the dysphagia except for hypertrophy of the cricopharyngeus muscle. It is interesting that the patient could swallow whiskey but was unable to take anything else by mouth. This was also true of 1 of the cases reported by Brunner,[3] in which he states, "the dysphagia was improved by drinking of whiskey."

CASE 2. E.R. (M.G.H. 785710), a 76-year-old woman, entered the hospital because of difficulty in swallowing of 3 years' duration. About 2½ years before admission an x-ray examination of the esophagus had revealed nothing ab-

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normal. Bronchoscopy and esophagoscopy at another hospital had also been negative except for bulging of the posterior wall of the hypopharynx. Bougienage had been carried out with the use of mercury and nonopaque bougies, No. 32 Fr. to No. 40 Fr.

The past history included removal of an osteosarcoma from the lower end of the tibia and a mastectomy on the right 27 years previously. The patient was known to have cardiac disease and had had repeated attacks of congestive heart failure. She was also blind and partially deaf. At the time of admission she was unable to take anything by mouth.

After treatment of the dysphagia, arteriosclerotic heart disease with atrial fibrillation and congestive heart failure, as well as a probable pulmonary infarct at the right base, barium-swallow examination was reported as follows:

> One teaspoonful of barium passed readily from the mouth into the laryngeal pharynx outlining normal-appearing valeculiae, pyriform sinuses and epiglottis. The bolus of barium did not pass into the esophagus, and a small amount trickled into the trachea. The examination indicates a satisfactory deglutition process, with apparent obstruction to the passage of the barium through the superior esophageal orifice.

Esophagoscopy was then performed under general anesthesia (nitrous oxide, Pentothal and Anectine). The larynx and hypopharynx appeared normal. There was so much spasm of the cricopharyngeus that esophagoscopy was not possible under local anesthesia. After good relaxation under general anesthesia it was still not possible to pass either the 9-mm. or the 8-mm. esophagoscope, apparently because of thickening and hypertrophy of the cricopharyngeus. The 7-mm. esophagoscope was then passed after slight delay, a No. 18 bougie being used as a guide. Except for slight reddening (which may have been due to recent use of a Levin tube) the esophagus appeared normal all the way to the cardiac orifice, which also appeared normal. There was some barium in the esophagus, and the lumen was not easy to find because it did not seem to dilate readily. Bougies No. 10 to No. 18, inclusive, passed readily into the stomach. When the instrument was removed the area of the cricopharyngeus was again carefully inspected and appeared smooth, with no evidence of tumor, extrinsic pressure or web. The findings were considered those of hypertrophy of the cricopharyngeus. No other lesion was demonstrable.

In spite of the dilatation of the cricopharyngeus by the passage of the esophagoscope the patient continued to be unable to swallow liquids or her own saliva. Nitroglycerin, inserted dry under the tongue, was of no benefit. She was seen in consultation by Dr. Sweet, who suggested a gastrostomy for feeding. Accordingly, 1 week after esophagoscopy, a Stamm gastrostomy was performed. After a somewhat stormy convalescence because of gastric bleeding she was discharged 2 weeks after the gastrostomy with instructions to report to the surgical outpatient department. This appointment was not kept, and she has not been seen or heard from since discharge.

Summary

Two cases suggestive of dysphagia due to hypertrophy of the cricopharyngeus muscle, sometimes called "hypopharyngeal bar" are reported. In 1 case the findings at autopsy tended to confirm this diagnosis, and in the other, the clinical findings were similar although positive histologic confirmation is not available.

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BY THE LONDON POST

Private Medical Practice — The Clinical Approach — Lecture Notes

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IT is difficult to assess the extent of private medical practice today, but it appears that whereas it is a diminishing factor in general practice, it exists to a considerable degree in consultant practice.

Since the introduction of the National Health Service an ever-increasing number of persons have signed on its list of general practitioners. There is nothing to prevent any general practitioner from taking private patients, but he may not charge fees to patients on his National Health Service list and he may not prescribe drugs on its forms to any patient who is not on his list. The effect of this regulation is to deny the private patient cheap drugs. The result is that many who would willingly pay their physician refuse to pay for expensive drugs and become State patients to avoid doing so. The majority of patients who do remain private are elderly, and they are not being replaced by members of the rising generation.

On the other hand, there are signs that private consultant and specialist practice is flourishing. Despite the gloomy prophets who were sure that the shutters would soon be up in Harley Street, this famous street is daily lined with the sleek, black limousines of the consultants and their patients, and the young specialist finds great difficulty in obtaining a consulting room in the area.

There are doubtless many causes of what appears to be a revival of private consultant practice. Many persons are insuring themselves and their families so that they can if necessary have private treatment from specialists; many people are still coming from abroad for private treatment, and many companies are paying for private treatment when their executives fall sick. Finally, there are many who still prefer to consult the specialist privately rather than in his crowded hospital clinic. So great indeed is the demand for private treatment from specialists that there is now a shortage of private beds. There are doubtless far fewer nursing homes than before the war, and in some cities in the North of England there are said to be no private beds at all. This has aggravated the situation in London, where there is often a considerable period of waiting for nonurgent admissions to private rooms. So serious is the position that a nonprofit-making organization has been set up for the purpose of bringing about a closer integration of existing facilities and of exploring the possibility of making more private beds available.

* * *

The medical curriculum is always under fire. It is everywhere acknowledged that the ever-increasing mass of information that the student is asked to assimilate is rapidly approaching what may be the saturation point of the average mind. When the emphasis is persistently on the purely scientific it is timely to have the importance of the clinical approach re-emphasized — although by those whom the young might tend to describe as the older physicians.

Dr. George Beaumont, in his presidential address to the Section of Medicine at the Royal Society of Medicine, stressed the importance of learning and practicing medicine at the bedside. He deplored the modern tendency for the clinician to be reduced to the status of a technician, and for true values to be lost under the jargon described as knowledge. He urged all doctors, in the words of Montaine, to be "gracious, gay and pleasing" in their first meeting with patients, and said that there was no place for the gloomy physician. He said that patients are filled with anxiety and in need of reassurance, and because of this the doctor should always be as easily accessible as possible. In the hospital this is sometimes difficult, especially in formal rounds, when the chief is surrounded by nurses, interns and residents, but the patient should never feel that he has ceased to be a patient and has merely become an object for discussion.

Turning to the vitally important matter of history taking, Dr. Beaumont spoke of the dangers of accepting a ready-made diagnosis or a history taken by another doctor. Accurate history taking, apart from questioning the patient, involves the exercise of observation, and it was only because Sir Arthur Conan Doyle had studied the way in which his Edinburgh teacher, Dr. Bell, cultivated the art of observation that he was able to portray Dr. Watson as such an astute clinician. Thus, in the *Blue Carbuncle*, he took one look at a bowler hat and reflected that "so large a head must contain brains."

Of investigations Dr. Beaumont said that these should remain ancillary aids to clinical diagnosis and that they should be carried out for the sake of the patient and not for the sake of the investigation. He was horrified at the modern tendency to order numerous investigations even before a provisional diagnosis is made — a practice that he described as decerebrate medicine. In concluding he asked quite bluntly that all doctors in their approach to their patients should be clinical and not cynical and that they should use their senses and never practice decerebrate medicine.

Dr. A. E. Clark-Kennedy, former dean of the London Hospital Medical College, also emphasizes the importance of the clinical approach in a recently published book, *Medicine in Its Human Setting*. In 22 short stories linked together by a doctor's practice and the hospital to which he refers his cases he describes a great many of the common medical hazards of life and their impact on the homes in which they occur. Thus, in 2 chapters, entitled "Advancing Age" and "Precarious Lives," he relates the vascular troubles of three brothers who eventually succumb to coronary thrombosis, cardiac failure and a cerebrovascular accident. In "Early Handicap" he speaks of a mother's life handicapped by mitral stenosis; in "Crowded Factory" he tells of tuberculosis, and in "Study in Tact" the doctor meets syphilis in high places. Because of his life-long experience and his depth of understanding of the human mind Dr. Kennedy has been able to paint into one picture the science and art, the mistakes and failures, the humor and tragedy of medical practice against the knowledge, tact and understanding it demands. In short, he has portrayed the art of practicing clinical medicine.

* * *

Students are usually less vocal than their teachers in their comments on teaching methods. Although they may display a great avidity for knowledge, they often lack the power to discriminate. This lack of appreciation of what is important in teaching was revealed in a letter that recently appeared in the *Times*.

A young graduate suggested that an important step forward in the academic field could be brought about by improved methods of lecturing in the universities. He thought that printed lecture notes should be handed to each student at the beginning of a session so that during lectures he would waste no time in taking notes. In subsequent correspondence his suggestion was violently opposed by several university teachers. One considered that students should be encouraged to absent themselves from any lecture that was merely a dictating session, and another pointed out that a good lecturer should try to avoid repeating himself, however often he gives a lecture, and that printed notes would simply tend to place him in a strait jacket. A lecture is not worth offering unless its object is to infect the students with the enthusiasm and outlook of the lecturer.

One of the aims of university life should surely be to teach a student to make his own selections of what is worth while and should stimulate his own reading and help him to cultivate the difficult art of thought. Spoonfeeding can never do this. Although this method is already practiced in some universities it is surely contrary to the primary purpose of education.

CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 41521

PRESENTATION OF CASE

A fifty-nine-year-old executive was admitted to the hospital because of peripheral arterial insufficiency.

About seventeen years previously the patient suddenly had severe shooting pain in both legs while walking. The pain was relieved with rest but a mottled discoloration of both legs persisted for a week. During the next three years the pain recurred three times at yearly intervals. Two years before admission he noted symptoms of intermittent claudication in the right leg. Femoral arteriograms nine months before entry demonstrated bilateral "blocks in the circulation." Some improvement was noted after a right lumbar sympathectomy four months later but subsequently the claudication became worse.

There was a history of oppression in the chest with effort and a diagnosis of a small coronary occlusion was made from an electrocardiogram about nine years before admission. The blood pressure at this time was 220 systolic. The patient denied any cardiac symptoms for the past one and a half years when his activity had been restricted because of claudication.

Physical examination revealed that the skin of the right lower extremity was warmer than the left. Save for the left femoral pulse, no pulses were palpable in the lower extremities. Examination of the heart was negative.

The temperature was 98.4°F., the pulse 80 and the respirations 14. The blood pressure was 210 systolic, 100 diastolic.

Urinalysis was negative; the specific gravity was 1.024. Examination of the blood revealed a hemoglobin of 14.8 gm. per 100 cc. and a normal white-cell count. The nonprotein nitrogen was 45 mg. per 100 cc. Prothrombin time was 12 seconds (normal, 13 seconds). An arteriogram showed probable thrombus formation within the left common iliac and right external iliac arteries and complete block of the left superficial femoral artery in its midportion (Fig. 1). There was reduction in the caliber of the lumen of the right superficial femoral artery at the midthigh. Slow renal excretion of Diodrast was noted and the left kidney was smaller than the right. An x-ray film of the chest showed multiple calcifications in both lung fields and a normal sized heart. The electrocardiogram was normal.

On the fourth hospital day, at operation the aorta was exposed with some difficulty because of a great deal of abdominal fat. A markedly arteriosclerotic aortic bifurcation containing an old mural thrombus and the right superficial femoral and both external iliac arteries were resected, with insertion of homologous arterial grafts. There was almost complete obliteration of the lumen of the right external iliac artery at its origin. An old thrombus occluded the distal portion of the right external iliac, the right common femoral, and the origins of the right superficial femoral and profunda femoris arteries. The right superficial femoral artery was patent distal to its origin. After thromboendarterectomy of the right common femoral artery a free flow of blood was obtained through the profunda femoris. The aorta, after being freed up, became completely thrombosed

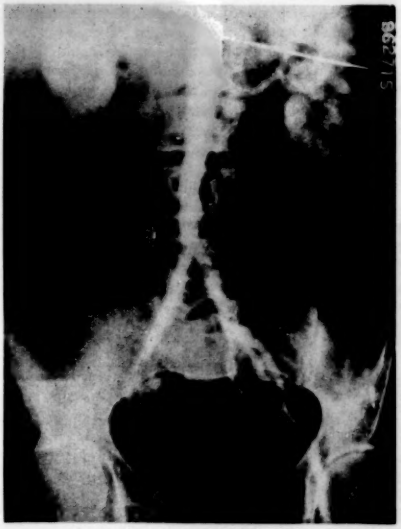

FIGURE 1. *Abdominal Aortogram, Showing Narrowing of the Distal Abdominal Aorta by Mural Thrombus and Evidence of Obstruction of the Right External Iliac Artery. Poor filling of the left common iliac and external iliac arteries, also the result of thrombus formation, is to be noted.*

and considerable secondary thrombus extended down into the iliac arteries. The thrombus was removed with some difficulty. Heparin was then instilled into the iliac arteries and the bifurcation graft was sutured in place. Atheromatous plaques were noted in the aorta proximal to the anastomosis. The renal arteries were not visualized. On the right side it was necessary to add two additional homografts in order to reach down to the superficial femoral artery. After completing the anastomoses, pulsations in the left femoral and right superficial femoral arteries were satisfactory. Because of thrombus formation at the thromboendarterectomy site, the right superficial femoral artery was ligated and divided just proximal to the distal anastomosis on this side. Bilateral lumbar sympathectomy was also done with removal of the second right and second and third left lumbar ganglia. Operating time was seven and a half hours. Pentothal-nitrous-oxide-oxygen anesthesia was used together with Anectine and Pontocaine catheter spinal. During the procedure the blood pressure varied between 100 systolic, 60 diastolic and 140 systolic, 80 diastolic. Thereafter it was stabilized at about 150 systolic, 90 diastolic. The patient was given 2500 cc. of whole blood and 925 cc. of plasma followed by 1000 cc. of 5 per cent dextrose in water. Urine output, which had been 1200 cc. and 1000 cc. during the two days preceding operation, was an estimated 100 to 200 cc. during the operation and it appeared grossly normal. After the operation there was no urinary output.

Postoperatively there were good femoral pulsations and a weak right popliteal pulse. About sixteen hours after the operation, the right popliteal pulse was no longer palpable, the right foot was cold, the left leg and foot were cold and cyanotic and the skin over the left buttock and thigh was mottled. The serum sodium was 133 milliequiv., the potassium 5.7 milliequiv., the chloride 93 milliequiv., and the carbon dioxide 24 milliequiv. per liter; the serum creatinine 4.3 mg. per 100 cc. The hematocrit was 41 per cent and the hemoglobin 14.2 gm. per 100 cc. The clotting time was 17 minutes. Direct and indirect Coombs tests were negative. Reoperation, at this time, showed the left common femoral artery and the left superficial femoral artery distal to its origin to be pulsating well as was the left renal artery, which was palpated. Exploration of the left popliteal artery showed no evidence of thrombosis. The peritoneal cavity contained an estimated 400 to 500 cc. of blood. Considerable oozing from raw surfaces was noted but no acute bleeding source could be found. The aortic graft seemed to be in excellent condition and all anastomoses were intact. The liver and spleen were normal. Operating time was two and a half hours and the patient received 1000 cc. of whole blood with 300 cc. of plasma followed by 700 cc. of 10 per cent dextrose in water. There was a twenty minute period of hypotension during which the blood pressure fell to 80 systolic with an unobtainable diastolic pressure. The pressure responded to ephedrine and thereafter was maintained from 110 systolic, 80 diastolic to 190 systolic, 120 diastolic. Postoperative physical examination showed mottled cyanosis over the sacrum and cold legs. The blood pressure was 140 systolic, 100 diastolic. On the next day the sodium was 133 milliequiv., the potassium 9.1 milliequiv., the chloride 87 milliequiv., and the carbon dioxide 23 milliequiv. per liter; the serum calcium was 7.2 mg. and phosphorus 13.1 mg. per 100 cc. Physical examination showed respiratory splinting, weak cough with difficulty in raising secretions, cyanosis, gasping respirations and obtundation. There was some improvement after bronchoscopy. During the day after the second operation the patient received 750 cc. of 10 per cent dextrose in water intravenously as well as antibiotic therapy, which had been given since the first operation. The blood pressure was in the range of 100 systolic, 60 diastolic. He died, still anuric, three days after the first operation. An electrocardiogram shortly before death showed marked peaking of the T waves.

Differential Diagnosis

Dr. Arnold S. Relman*: This fifty-nine-year-old obese hypertensive man obviously had peripheral arteriosclerosis obliterans and a history suggesting coronary artery disease. He became totally anuric after extensive resection of the bifurcation of the aorta and the common iliac arteries. He died three days after operation still anuric, with, and quite possibly of, potassium intoxication. The diagnostic problem is essentially one of the etiology of sudden total renal failure that developed at the time of operation. In this sort of clinical problem we must consider first the possibility of extrarenal factors causing oliguria and renal failure. The first extrarenal factor that we ought to consider is the possibility that sustained shock—relative or absolute—so reduced the filtration pressure at the glomerulus that urine could not be formed; this could conceivably occur without any structural damage to the kidneys. The patient was in shock during the operation and terminally but otherwise the blood pressure was not particularly low. However, he was markedly hypertensive before operation and did suffer a considerable fall in the blood pressure from his preoperative levels. It is possible that with pre-existing vascular disease in the kidneys reduction of blood pressure of this magnitude could reduce filtration in the kidneys without causing structural renal damage. However, I think this is unlikely. In the first place, he remained totally anuric for three days. Hypotension severe enough to stop filtration for three days would probably have resulted in structural change in the kidneys. In the second place no urine was passed despite the fact that the blood pressure was relatively high for some periods of time postoperatively.

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The second extrarenal factor that might cause acute renal failure with oliguria is severe electrolyte depletion with dehydration. I think I can dismiss that possibility more confidently than the first one. The patient was not apparently dehydrated or hyponatremic; the serum sodium was slightly low but he had received adequate fluid therapy. Furthermore, this degree of renal insufficiency, with total anuria for three days, cannot be caused by dehydration or hyponatremia alone. There would have to have been an additional factor, such as shock, which I have already considered, or else structural damage to the kidneys.

The third extrarenal possibility, which always needs to be considered clinically, is postrenal obstruction. There was no evidence of a lesion in the genitourinary tract that might have predisposed to obstruction, such as a stone or a stricture. At this point, I think it would be advisable to consider the evidence relating to the preoperative status of the genitourinary tract. May we look at the aortograms?

DR. JOSEPH HANELIN: The aortogram shows diffuse opacification of both kidneys and patent renal vessels (Fig. 1). I shall not go into details about the abnormality of the aorta, which has been well described in the protocol. The single abdominal film made at some unspecified interval after the aortogram, shows both kidneys to be functioning without any obvious morphologic abnormality of the collecting systems although the calyceal detail is poor. There is nothing to suggest any blockage to the ureter. One kidney is smaller than the other, but is not appreciably reduced in size. The films of the chest are not particularly helpful; the lungs and heart are normal.

DR. RELMAN: This is very useful and pertinent information. Renal function prior to the operation was apparently normal or nearly normal. The urinalysis was negative and the urine could be concentrated to a specific gravity of 1.024. The blood nonprotein nitrogen was not obviously elevated. Both kidneys appeared to be normally vascularized; no preexisting vascular damage to the large vessels of either side was apparent. Dye was excreted about equally from both sides and no stone or obstruction in the lower urinary tract was evident. Nevertheless I cannot rule out the possibility of postrenal obstruction as a cause of the renal insufficiency. For example, one must consider the possibility of trauma to the ureters during operation. Another possibility is obstruction as a result of gross bleeding into the kidneys. He appeared to have some sort of mild hemorrhagic diathesis after the operation, presumably related to the large amount of banked blood that he had received, or to the extensive extravascular coagulation that was occurring. Possibly with bleeding into the kidney, clots could have formed in the ureters, obstructed them and stopped the flow of urine. But usually with anuria due to a blood clot in the ureter there is colic and some bleeding prior to shutdown; I think this possibility is unlikely.

Having considered the extrarenal causes of anuria I now have to discuss the possibility that the kidneys themselves were damaged at the time of the operation. Several types of renal disease can result in abrupt loss of renal function with varying degrees of oliguria. Two disease entities I shall at once dismiss as unlikely: acute glomerulonephritis and necrotizing papillitis. These both may cause acute renal failure with oliguria, but in this case there were no clinical signs or symptoms to suggest either infection or acute nephritis. Furthermore the clinical picture was much more accelerated and the onset of anuria more abrupt than one sees with acute nephritis or necrotizing papillitis.

A third possibility — infarction of the kidneys — deserves much more serious consideration. Both kidneys appear to have been functioning prior to operation. Conceivably this patient could have suffered bilateral arterial infarction of the kidneys. He had the background for it. He had extensive atheromatous disease of the aorta. Furthermore at operation the atheroma were observed to extend above the level of the resection, and during the operation new thrombi formed. It seems reasonable to consider the possibility that thrombi might have formed in a retrograde fashion and extended into one or both of the renal arteries. However, at the second operation the left renal artery was seen to pulsate normally, so I must assume that rules out the possibility of infarction on the left side. No mention was made of the right renal artery. I wonder if I might have more specific information about that?

DR. ROBERT S. SHAW: I was not present at the operation but I was surprised that the surgeon was able to feel the left renal artery because with that particular exposure it is high and obscured by overlying structures. The left is easier to feel than the right; I suspect that the right just was not felt.

DR. RELMAN: The possibility remains, therefore, that the right kidney was infarcted. But if the left kidney was not, one would think that the patient should not have become totally oliguric unless something else had happened to the left kidney.

Venous infarction of the kidneys is rarer than arterial infarction and usually occurs on a background of previous sepsis or pre-existing thrombophlebitis of the large veins of the abdomen. The clinical background in the patient under discussion did not suggest either sepsis or pre-existing thrombophlebitis; therefore I think that bilateral renal venous infarction can probably be dismissed.

Two other possible causes of acute renal failure with oliguria remain to be considered. The first is acute tubular necrosis or so-called lower-nephron nephrosis. Many factors in this story might predispose to the development of acute tubular necrosis. The patient was in relative shock for some time; he had pre-existing vascular disease and he received anesthesia for a long period of time. All these might

combine to result in a critical reduction of blood flow to the kidneys, with necrosis of tubular epithelium and abrupt onset of renal failure. He received a great deal of blood, so the possibility of a hemolytic transfusion reaction must be considered. The negative direct Coombs test seems to militate against that possibility, as do the absence of hemoglobinemia and of hemoglobinuria in the early phase. I think the possibility of acute tubular necrosis due to any cause should be considered with some skepticism, however, because of the fact that the patient was totally anuric. Total anuria is not commonly seen with acute tubular necrosis. The patient usually puts out a small amount of urine, which tends to increase slowly with time.

The sudden development of total anuria suggests the possibility of bilateral cortical necrosis, which can be produced by many of the same factors causing acute tubular necrosis. The critical physiologic change that predisposes to the necrosis of the cortical tissue appears to be a sudden reduction in the blood flow to the cortical nephrons, thought to be the result of spasm or thrombosis in the intralobular and arcuate arterioles. It seems to me that the history is in many ways consistent with, and suggestive of, bilateral cortical necrosis. The patient undoubtedly had a great deal of pre-existing vascular disease in the kidneys and elsewhere; he had been moderately to severely hypotensive and then he suddenly stopped making urine and remained totally anuric. That sort of picture suggests bilateral cortical necrosis. Bilateral cortical necrosis can occur as the full-blown lesion, with extensive confluent necrosis of the cortex or it can occur as a patchy process, in association with tubular necrosis. Where the disease entity that we call acute tubular necrosis ends and bilateral cortical necrosis begins is difficult to say. It seems to me that it may be artificial to make any distinction between the two processes. Experimental work would appear to indicate that the more severe the ischemia to the cortex, the more extensive the necrosis becomes, and with the severest degree of ischemia the necrosis becomes confluent and involves structures other than the tubular epithelium — that is to say, it begins to involve glomeruli, interstitial tissue and blood vessels and finally ends in cortical necrosis.

In summary I think that the patient probably suffered an acute renal insult at the time of operation and that the cause of the acute renal insult is most likely to have been bilateral cortical necrosis, or one of its variants. Arterial infarction of both kidneys appears to be ruled out by the good pulsation in the left renal artery; the possibility still remains, however, that the right kidney was infarcted and that the left kidney became ischemic as the result of reflex changes or possibly as the result of tubular necrosis. On the basis of probability I shall choose cortical necrosis with death due to potassium intoxication.

DR. RICHARD B. COHEN: Are there any comments or questions?

DR. WARREN POINT: Would Dr. Relman care to comment about the very high phosphorus and high potassium in three days? Do you think that breakdown of muscle in the tissues contributed to those high levels?

DR. RELMAN: I think that is quite likely. Ordinarily the serum potassium does not rise this abruptly with acute renal shutdown. I think the fact that he had severe ischemia of muscle undoubtedly resulted in the release of large amounts of potassium. It is also possible that the many blood transfusions may have contributed to the elevation of the serum potassium.

DR. POINT: Could myoglobin have plugged the tubules?

DR. RELMAN: I think it is possible that this was an additional factor, but he became anuric abruptly at the time of operation; therefore I am inclined to believe that something happened at operation before there was extensive death of muscle tissue.

DR. BENJAMIN CASTLEMAN: What do you think happened at operation that might have produced the tubular necrosis?

DR. RELMAN: According to the protocol the blood pressure during the operation varied between 100 and 140 systolic and 60 and 80 diastolic. That gives an estimated mean arterial pressure of somewhere between 75 and 110, whereas preoperatively the estimated mean arterial pressure was 140 to 145. I should say that in the presence of pre-existing vascular disease, that degree of relative hypotension possibly combined with other factors — such as deep prolonged anesthesia — would be enough to produce fatal renal ischemia.

DR. COHEN: Dr. Tuttle, what is your opinion?

DR. ELBERT P. TUTTLE, JR.: Our impression was that he had had a vascular accident to the kidneys, particularly because of the complete anuria. We believed that he had either occlusion of the major renal artery on one side with secondary spasm and anuria on the other, resulting in necrosis of the tubules or the cortex or both; or that he had had multiple emboli that occluded both kidneys.

DR. SHAW: I think it is important to round out the record by mentioning the possibility that he had significant renal damage from the aortogram itself, which was done three days before the operation. We have had in this hospital two cases of severe, lasting oliguria following an aortogram in patients with lower aortic occlusive disease. I am told that routine studies of renal function after aortography commonly reveal evidence of mild temporary renal damage. I think it is unlikely in this particular case since he demonstrated good urinary output between the aortogram and the operation.

This was certainly a difficult, trying technical exercise for the surgeon. When one embarks on an effort to re-establish arterial continuity in a case like this, he cannot stop at any given time or stage of the

operation, as he can in other abdominal surgery, because if he does he may cause a limb in the patient to become gangrenous. This can mean, as in this case, that he spends a great deal of time arranging and rearranging the arterial plumbing until he establishes a good flow. It has proved worth while, incidentally, to re-explore these patients in the early postoperative period if it appears that they have had thrombosis in the grafts. We have been able to salvage a high percentage of potential failures in this manner. In spite of the length and difficulty of this sort of surgery and of the fact that all these patients have generalized arteriosclerosis, the mortality has been surprisingly low. To my knowledge this is only the second death in this hospital after an elective operation of this nature, and there have been a great number done.

I might mention that the blood bank was very sensitive to the possibility that the patient under discussion might have had an incompatible transfusion and for that reason secured blood at postmortem examination. The Coombs test was negative and there were no demonstrable antibodies to any of the specific red cell antigens.

DR. COHEN: I notice, Dr. Shaw, that the internal hypogastric vessel on the right was occluded during the course of the operation. Can that be done with impunity?

DR. SHAW: Usually it can in patients with occlusive arterial disease, since they have rather extensive collateral circulation that has gradually developed from the inferior mesenteric artery and other sources. That is not true in patients with aortic aneurysm alone without occlusive disease who have a widely opened hypogastric artery; in such patients an effort must be made to restore circulation to the hypogastric artery. Cases of perineal necrosis following bilateral hypogastric arterial ligation for the aneurysms have been reported.

CLINICAL DIAGNOSIS

?Tubular necrosis.
?Multiple emboli to kidneys.

DR. ARNOLD S. RELMAN'S DIAGNOSIS

Bilateral renal cortical necrosis.

ANATOMICAL DIAGNOSES

Renal infarction bilateral, recent, due to multiple embolization of atheromatous thrombi during aortic resection.

Atherosclerosis, severe, aorta and renal arteries.

Operations: aortic resection and graft for aortic thrombosis, femoral artery exploration.

PATHOLOGICAL DISCUSSION

DR. COHEN: The significant pathology was present in the lower aorta and the kidneys. The entire aorta

FIGURE 2.

was extensively atherosclerotic, the process being more severe in the lower abdominal region and particularly so around the mouths of the renal arteries. In this area atheromatous ulcers were prominent. These were lined by grumous material made up largely of cholesterol, fibrin and old blood clot (Fig. 2). The major renal vessels were patent but narrowed. The graft itself was intact and patent as were all the major vessels dissected. The kidneys were reduced in size and granular, probably the results of the old arteriosclerotic process. Superimposed on this, however, was an obviously acute change that consisted of a yellowish mottling. This was focal in areas in which case it was surrounded by a reddish congested zone, but in other areas it was coalescent and occupied a considerable volume of renal tissue both cortical and medullary. Both kidneys appeared equally involved. On microscopical examination of the kidneys it was found that many vessels from arcuate arteries down to the smaller interlobular arteries were plugged and completely occluded by atheromatous material (Fig. 3) of the same type as that found loosely adherent to the wall of the aorta at the origin of the renal arteries. The mottled yellow areas noted grossly proved on microscopical

examination to be extensive infarction undoubtedly secondary to this diffuse embolization to renal vessels. The sequence of events that appears to be most likely

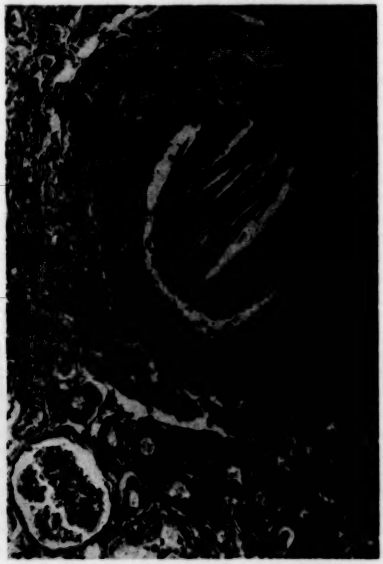

FIGURE 3.

is that during the operation there was sufficient manipulation of the aorta to loosen atherosclerotic material from its wall in the region of origin of the renal arteries. This resulted in showers of emboli to the smaller renal arteries, consequent renal infarction, which was extensive, and death in renal failure.

CASE 41522

PRESENTATION OF CASE

A three-week-old female infant was admitted to the hospital because of abdominal distention.

Three days before admission abdominal distention was first noted. On the next day the infant began to vomit breast feedings. A previously dry umbilical stump was found to be moist, respirations became grunting and the appetite decreased. During the day before entry the temperature ranged from 100.2 to 102°F. There was no diarrhea; stools appeared normal.

The baby's mother was forty-two. Delivery was at term and normal. The mother had received penicillin therapy for recurrent renal disease during the pregnancy, which was otherwise uneventful. This was the mother's first pregnancy. The infant was Rh positive and the mother Rh negative. Because of the possibility of hemolytic disease that might require transfusions the cord was left long at birth. This necessity did not arise. Scattered, large cutaneous bullous lesions, which later cleared, were noted at birth. During the first week of life the infant's weight rose to 3.7 kg. At admission it was 3.65 kg.

Physical examination showed a critically ill, dehydrated marasmic baby with grunting respirations. There was no jaundice. The upper respiratory tract was normal. No cough was noted. The heart and

FIGURE 1. *Anteroposterior Film of the Chest and Abdomen, Showing Evidence of Increased Intra-abdominal Fluid, with Bulging Flanks and Mildly Distended, Gas-Filled Loops of Small Bowel.*

lungs were normal. The abdomen was nontender, distended and tense, with dilated superficial veins having a cephalad direction of flow. A fluid wave was present. The liver edge was palpable 4 cm. below the right costal margin; the spleen was not felt. There were no masses. One observer heard muffled peristaltic sounds; another heard none. The umbilicus was partly everted, somewhat reddened, and ecchymotic without purulent drainage. No local heat was present. Unobliterated hypogastric arteries, which could be probed to the superior pubic rami bilaterally, revealed no drainage or communication with the

peritoneal cavity. A 1-cm. scar, the remains of a bullous lesion, was present on the posterior aspect of the right thigh.

The temperature was 99°F., the pulse 130 and the respirations 24.

The urine gave a + + + test for albumin and a + + reaction to the Harrison spot test. Examination of the blood revealed a hemoglobin of 14 gm. per 100 cc. and a white-cell count of 2700, with 50 per cent neutrophils, 45 per cent lymphocytes and 5 per cent monocytes. X-ray films demonstrated slightly emphysematous lungs and a normal heart. Gas was present in the small and large intestines. The configuration of the small intestine was slightly unusual, but no definite evidence of obstruction was noted. Ascitic fluid was present (Fig. 1).

In three abdominal paracenteses a total of 200 cc. of purulent bright yellow fluid, which contained numerous phagocytic mononuclear cells some of which showed erythrophagocytosis, was obtained. A smear showed numerous gram-positive cocci in chains. Culture grew out moderate alpha hemolytic streptococci and rare *Staphylococcus albus*.

In spite of antibiotic therapy and intravenous fluids the patient died eighteen hours after admission.

Differential Diagnosis

Dr. Leo B. Burgin*: Three days before admission abdominal distention was noted. The baby vomited the next day. No note is made of whether this vomiting was projectile or whether it continued up to the time of admission or occurred only at feeding times. Vomiting and distention are frequent findings in any disturbance in early infancy. They are not diagnostic of any one disease or group of diseases but may result from a host of causes either enteral or parenteral in origin: feeding problems, infections and congenital abnormalities of the gastrointestinal tract such as stenoses, atresias, duplications and malrotations. The continued presence of normal stools and a grossly normal gas pattern by x-ray examination would be evidence against complete obstruction.

May I see the abdominal films?

Dr. Joseph Hanelin: The lungs are clear and somewhat hyperaerated. The heart is of normal size. There is gas in the stomach and small bowel, but no evidence of abnormal distention. There is also indication of increased fluid within the peritoneal cavity (Fig. 1). The liver appears enlarged; the spleen cannot be outlined.

Dr. Burgin: I think I can dismiss the feeding problem because the baby was breast fed and hardly likely to present so severe a picture of malnutrition.

Duplication of various portions of the gastrointestinal tract may be responsible for intermittent obstruction. These enteric cysts dilate in response to accumulation of secretion from their mucosa and compress adjacent normal bowel. In malrotation of the cecum the obstruction occurs usually at the level of the duodenum resulting in dilatation of that structure and of the stomach as well. Vomiting, if severe enough, may empty the stomach so that dilatation is not visible by x-ray examination. The protocol says nothing more about the vomiting. Subsequent events would appear to make the findings of such anomalies unlikely.

If there was more emphasis on vomiting in the protocol we should have to consider pyloric stenosis. This disturbance occurs four times more often in males than in females. The time of onset is likewise early for the usual case.

Sepsis in the neonate may occur without a dramatic onset. Indeed the usual criteria for infection may be wanting. The temperature may be slightly increased or normal as noted here. Leukocytosis, though usually present, may, when the infection is an overwhelming one, be absent. The marked leukopenia of 2700 reported here with 50 per cent neutrophils suggests severe overwhelming infection rather than a viral disease. There was nothing to suggest a blood disturbance. The hemoglobin of 14 gm. was high and must have represented a marked degree of dehydration. Jaundice was not recorded although there was a report of a + + Harrison spot test for bile in the urine. This undoubtedly represented liver damage probably from sepsis. Infectious hepatitis or homologous serum hepatitis is extremely unlikely on the basis of data presented. Jaundice occurs with great ease at this age. Obstructive jaundice should very quickly give rise to visible icterus and easily demonstrable bile in the urine.

If I assume for the moment that infection was present, what was the site of entry? At this age portals of entry for bacteria are the respiratory tract, the gastrointestinal tract, the skin and the stump of the umbilicus.

Grunting respirations and emphysema noted in the x-ray examination suggest bronchiolitis, which is distinctly a disease of the young. However, these infants have severe distress and one does not get the impression of that type of difficulty here. With severe infections of any kind in an infant of this age, grunting respirations often occur.

The presence of normal stools implies normal digestion. Infection of the bowel does not appear likely. I suppose one would not dare omit mention of typhoid fever in a case of abdominal distention and leukopenia. The absence of enlargement of the spleen, lymphocytosis, rose spots and a likely source of infection makes this diagnosis unlikely.

I come now to a consideration of the skin as a possible source of infection. Bullous lesions were reported at birth. I believe such an early appearance of lesions would be most unusual for impetigo of the newborn (pemphigus neonatorum). These lesions were healed by the time of admission. This too would

*Physician to Children's Medical Service, Massachusetts General Hospital.

be unexpected in an untreated case. Epidermolysis bullosa is unlikely. The bullae in this disease recur quite persistently. The skin of the newborn infant may respond with bullous formation to trauma and irritation from urine and stool. I suspect that this was the situation here.

I note that the mother received penicillin during pregnancy. I doubt whether the skin lesions could be in consequence of transplacental passage of penicillin and subsequent drug eruption in the child. I learned last night at an allergy meeting that penicillin can be detected in the milk of cows given this antibiotic for the treatment of mastitis. I suppose the same thing is possible in the case of a nursing mother. This is pure speculation and probably does not enter into the picture here.

I am left, by exclusion, with the umbilicus as the most likely source of infection. The cord had been left long at birth because of the possible need for an exchange transfusion. Undoubtedly during the first day of life it was kept moist at least until the necessary laboratory work was completed. This meant that a longer period of time than usual elapsed before the cord mummified and that at the same time a larger area of cord was exposed, inviting infection. The umbilical stump, which had been dry, was found moist, reddened and without discharge. The local appearance of the stump may be unexciting even though severe infection is present underneath. Spread of infection usually takes place via the umbilical vein or arteries. The hypogastric arteries were probed and no evidence of pus or connection with the peritoneal cavity was found. The large liver, distention, ascites and dilated veins of the abdomen suggest portal obstruction. This event could have taken place as a result of a thrombophlebitis of the umbilical vein extending into the portal system secondary to an omphalitis. The umbilical vein and arteries are separated from the peritoneum by a very thin aerolar tissue. Infection (as was evidenced here by the presence of chains of cocci on smear of the peritoneal fluid) can easily break through.

To recapitulate, this infant had an unrecognized infection of the umbilicus that led to a thrombophlebitis of the umbilical vein and portal vein thrombosis with extension of infection into the liver. Ascites, secondary peritonitis and septicemia followed.

DR. BENJAMIN CASTLEMAN: How often do you see omphalitis nowadays?

DR. BURGIN: We have seen this extremely rarely in the last twenty years. I do not think that more than 3 or 4 cases have been reported from the Children's Medical Center since 1935, after the arrival of the sulfa drugs.

DR. JACOB LERMAN: How often do you see bullous lesions in the newborn?

DR. BURGIN: The skins of newborns react with bullae to almost any sort of trauma or irritation but if it is due to impetigo (a streptococcus or staphylococcus infection) it persists for several days.

DR. LERMAN: One wonders if the lesion present on admission was evidence of bullous impetigo.

DR. BURGIN: Bullous lesions in epidermolysis bullosa occur early. We have actually seen them at the time of delivery.

DR. EDGAR B. TAFT: Is not omphalitis rare at the age of three weeks?

DR. BURGIN: Yes; that disturbed me. I suppose since the cord was long, it may have persisted over ten days. Infection may have been present days before she had any systemic signs.

CLINICAL DIAGNOSIS

Omphalitis, with portal vein thrombosis.

DR. LEO B. BURGIN'S DIAGNOSES

Omphalitis, with portal vein thrombosis.
Peritonitis.

ANATOMICAL DIAGNOSES

Omphalitis, with pylephlebitis and peritonitis.
Septicemia, with microscopic abscesses in kidneys.

PATHOLOGICAL DISCUSSION

DR. TAFT: This child had exactly what Dr. Burgin predicted — an omphalitis, with spread of infection to the portal vein and obstruction of the portal vein by purulent material. At the time of autopsy there was no apparent thrombus and yet it would be difficult to say that there had not been thrombus, which had become infected and at the time of autopsy was soft and diffluent and not adherent to the vein wall.

The umbilical vein in the ligamentum teres was occluded distally. However, proximally the lumen of the umbilical vein was patent and filled with purulent material, which extended to the portal vein and also into the splenic and the superior mesenteric veins. A section from the umbilicus showed a small subcutaneous abscess. There was marked acute and chronic inflammation of the skin surface in this area. The slide from the ligamentum teres showed a vein that was full of purulent exudate. The primary infecting agent in this patient was a nonhemolytic streptococcus, which was possibly fecal in type. Sections from branches of the portal vein within the liver and from the superior mesenteric and splenic veins contained small amounts of purulent material. Their walls were markedly edematous and somewhat necrotic. The abdominal cavity was full of fibrinopurulent exudate, with much gray-green fibrinous material binding loops of bowel together. Microscopically there were small abscesses in the kidneys, — which would be evidence for septicemia, — which this pa-

tient undoubtedly had, although the blood cultures made post mortem were sterile.

The reason I asked about the age of the patient is that Potter* in her book on the pathology of the fetus and the newborn says that it almost always occurs within three to five or seven days of birth and that death occurs within the first ten days of life, rather than in the somewhat delayed period such as was seen in this baby.

DR. BURGIN: It is possible that the fact that the cord was left long may account for the time element.

A PHYSICIAN: We consider this a curable disease. Could a normally observant mother have noted that the child was ill earlier than this mother did?

DR. TAFT: According to what I have read, the inflammation and infection of the umbilicus often may be fairly unimpressive even in the presence of obvious systemic disease. One gets the impression that the mother may not have been very observant.

DR. CASTLEMAN: What antibiotics were used?

A PHYSICIAN: Erythromycin and Chloromycetin.

DR. TAFT: According to the post-mortem culture, the sensitivity of the organism to penicillin was not great, but it was sensitive to streptomycin, Chloromycetin, neomycin and Furacin. It was not sensitive to polymyxin, bacitracin or Aureomycin.

DR. WARREN POINT: Why did the surgeons have the artery probed?

DR. RICHARD B. KEARSLEY: The surgical consultant suggested that we pass a probe into the hypogastric artery for the possibility of a pus cavity that could be aspirated. We passed a small probe, which went down very easily.

DR. TAFT: The distal umbilical vein was thrombosed and organized in the section, just as it was on gross examination. The hypogastric arteries contained purulent exudate and colonies of cocci could be seen in this.

*Potter, E. L. *Pathology of the Fetus and the Newborn.* 574 pp. Chicago: Year Book Publishers, 1952.

MASSACHUSETTS PHYSICIANS ART SOCIETY

42. *Trojan Horse*

Hammered Copper by

JACOB W. HITE, M.D.

Medical Staff, Massachusetts Women's Hospital

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THE HOUSE OF DELEGATES

FROM Tuesday, November 29, through Thursday, December 1, Massachusetts physicians had a unique opportunity not only to see the House of Delegates of the American Medical Association at work but also to participate in its deliberations.

Despite the widespread opinion that its policy is dictated by a handful of medical politicians in Chicago, the sole policy-making body of the Association is the House of Delegates. Except in an emergency neither the Board of Trustees nor the officers have any right or authority to establish policy although they may and do recommend courses of action to the House. Actually, a prime function of the Board of Trustees and the officers is to implement policies established by the House.

Most of the members of the House of Delegates are elected by the state and territorial medical societies on the basis of 1 delegate for each 1000 members of the Association or fraction thereof. The House meets regularly twice a year, and although it may meet in special session, it rarely finds it necessary to do so. During a typical meeting, the Delegates consider reports submitted by the Board of Trustees, the councils and the officers of the Association and resolutions introduced by delegates. In accordance with customary procedure each report and each resolution is referred to an appropriate reference committee. Any member of the American Medical Association is privileged to appear before any reference committee and to express his views concerning any matter that the committee has before it. When the reference committees complete their hearings they each prepare a report on the respective items assigned to them, and it is this report that goes to the floor of the House for adoption, rejection or modification.

At the recent Boston session of the House more than 30 reports were submitted by the Board of Trustees, the councils and the officers of the Association, and more than 50 resolutions were introduced by delegates. Out of this welter of material came the reference-committee reports that resulted in various actions, a few of which are reported below.

Among others was the adoption of a substitute resolution proposed by the Reference Committee on Legislation and Public Relations, stating the following policy:

> That the American Medical Association reiterate in the strongest possible terms its determination to resist any encroachment upon the American system of medical practice which would be detrimental to our patients, the American people;
>
> That the American Medical Association urge and support the creation of a well-qualified commission, either governmental or private or both, to make a thorough, objective and impartial study of the economic, social and political impact of Social Security, both medical and otherwise, and that the facts developed by such a study should be the sole basis for objective non-political im-

provements to the Social Security Act, for the benefit of all the American people;

That the American Medical Association pledges its wholehearted cooperation in such a study of Social Security in the United States, and will devote its best efforts to procuring and providing full information on the medical aspects of disability, rehabilitation and medical care of the disabled, and

That copies of this resolution be transmitted to the President of the United States, to all members of the Cabinet, to all members of the Congress, and to all constituent state medical associations.

In another action the House recommended that state societies poll their entire membership on the question of the inclusion of physicians in the Old Age and Survivors Insurance provision of the Social Security Act and transmit the results of the poll to the Board of Trustees.

Actions were taken to encourage the formation of departments of general practice in each medical school and to discourage the restriction of hospital privileges for general practitioners as a class, regardless of their individual professional competence. Guides for grievance or mediation committees were approved, and the Committee to Recommend Guides for Grievance or Mediation Committees was commended for its "superb approach to this problem."

Among various miscellaneous actions the House recommended that the trustees consider an increase in dues, with the increase designated for contribution to the American Medical Education Foundation; it approved the appointment of a committee of the Association to study the prevention of highway accidents; it approved a recommendation of the Board of Trustees that the State Journal Advertising Bureau be separated from the American Medical Association and be given full autonomy; it congratulated the physicians of Iowa for their efforts in supporting the position that the practice of medicine is the right of the individual; and it approved the selection of Minneapolis for the 1958 Clinical Meeting and of Chicago for the 1960 Annual Meeting.

ON BEING RESOLUTE

THE philosophy of the resolution presents an annually recurring phenomenon that each year deserves a fresh and unbiased scrutiny. For the resolution, conspicuously seasonal in its flowering although usually of brief duration, has come in for a considerable outlay of kindly humor each January because the natural counterpart to the making of a resolution is the breaking of it. This is not bad; it merely shows that the heart, however faint, is in the right place and it makes the resolution that is resolutely kept stand out like the beacon that once topped Beacon Hill, in Boston.

Compromise being perhaps the crowning glory of human relations, it becomes obvious that resolutions need not be consistently kept or consistently broken. Like almost everything else on earth they need not operate on an all-or-none law. Three per cent interest on an investment is only half as much as the traditional six, but it is infinitely more than nothing.

It must also be apparent that the wise way to manipulate the problem of resolutions is the cozy one; if no announcements are made regarding them and there is no publicizing of them, one may get credit for keeping them if there is any improvement in one's performance, even if it had nothing to do with the New Year and no resolutions had been made. Equally desirable, one's annual failures need not have attached to them the added onus of a resolution broken.

The penalty of putting one's hopes and fears and cherished ideals on paper, and publishing them, as an editorial writer is almost compelled to do, invariably lays him open to the swift and deadly rebuttal. It can happen here, too, and curiously enough many editors never get entirely hardened to the return of the boomerang.

Nevertheless, the ending of the year is the natural time at which to strike a balance. It is the time for adding up the successes and subtracting the failures of the old year, and for announcing the hopes and intentions for the new. It is the time when resolutions should be made, regardless of their frangibility.

Through 1955 the *Journal* and its smoothly coordinating printers have maintained the distinction of meeting its production deadline utterly. It has been off the presses and ready for delivery each week on the date of publication. From that point on the story is often a different one, owing to the vagaries of mail delivery and an appalling number of address changes, especially in the younger, shifting groups of subscribers, composed of students, house officers and residents and those in military service. These difficulties, on which much study and hard work are being expended, may be partly offset by the fact that the subscription rate has not changed in seven years and is only $3.00 more than it was thirty-five years ago.

The temperamentality of postal authorities in other countries as well as this one is illustrated by the sudden reversal last year of a well established flow of *Journals*, when those directed to the Royal Society of Medicine on Wimpole St., in London, began to come back from the post office around the corner from the Society marked "Moved and left no address."

The circulation of the *Journal* is nevertheless a matter of considerable satisfaction, for it touched 39,000 last month, all told, of which nearly 25,000 were independent subscribers paying full price, and more than 7000 were students. This represents a total gain during the year of close to 7000. Over 500 manuscripts of original articles were submitted independently, of which approximately half were accepted.

The most perplexing problems of management have related to the accurate and prompt fulfillment of

subscriptions, the screening of advertising material and the earnest — and sometimes successful — efforts to persuade a few less discerning manufacturers to look at ethics the way the doctors try to look at it — or is it them?

If resolutions in the way of improved performance on the part of management and editing were to be ventured, they would include an unremitting effort to get each issue into the hands of all subscribers as accurately and as promptly as possible, with the cooperation of the subscribers in the matter of prompt and accurate reporting of breakdowns in delivery and changes of address. They would include an increasingly realistic and frequent appraisal of advertising copy — always a vulnerable point — and a stern but not a cruel attitude toward that particular form of research that seems to result in constrictor-like bodies of references dragging their sinuous tails through yards of the most expensive type of composition.

Perhaps it is not too much to expect from the authors of such solicited material as progress reports that they make — and keep — their own resolutions regarding the sanctity of deadlines, promising not that which they cannot fulfill. For the world is too much with them, and they still lay waste their powers.

And so, to all colleagues in the making of resolutions, a Happy New Year and better luck this time!

ASSESSMENT OF PREDNISONE

THE *Journal*, in an editorial published on November 24, 1955, called attention to the results of a controlled study of the comparative value of cortisone and aspirin in early cases of rheumatoid arthritis. From the results of this study, which was carried on over a period of two years, the investigators concluded that "for practical purposes, there has been remarkably little to choose between cortisone and aspirin."

Elsewhere in this issue the use of a new adrenocortical steroid, prednisone, is reported. Like many of the early accounts of ACTH, cortisone, hydrocortisone and other steroids, the presentation suggests that the new preparation is less toxic and more effective than those that have preceded it. Until a controlled study becomes available, there is still the possibility that, like its predecessors, prednisone will be simply another and more expensive substitute for aspirin, at least in the treatment of rheumatoid arthritis; consequently, its relative effectiveness, cost and toxicity, as compared with those of aspirin, are still to be assessed.

ANCHORS AWEIGH

THE elevation in November of Dr. Benjamin Tenney, Jr., to the rank of rear admiral in the Medical Corps of the United States Navy will be thoroughly approved in this area. Admiral Tenney, formerly a reserve captain, thus becomes the first naval reservist to attain this rank in the First Naval District, and the fourth in the history of the Corps.

Dr. Tenney, professor of gynecology and obstetrics at Boston University and director of the Department of Obstetrics and Gynecology at Boston City Hospital, has been a frequent contributor to the *Journal*. He started his military career as an ambulance driver with the French Army in World War I, and later was commissioned second lieutenant in the Army of the United States at Plattsburg in 1918. His subsequent career included graduation from Dartmouth College and Harvard Medical School and the establishment of a practice in Boston. He joined the Naval Reserve in 1935.

An obstetrician by choice and training, Dr. Tenney assisted in the delivery of Guadalcanal, later becoming chief of surgery of Fleet Hospital No. 5 in New Caledonia.

ENTERTAINMENT BY THE MEDICAL FACULTY OF HARVARD UNIVERSITY.

Another elegant entertainment was given on Saturday evening by the Faculty of the Medical College to the students attending lectures. A large number of physicians of this city and the vicinity were also present. The occasion was a most interesting one, and the guests of the faculty separated after having passed a delightful evening.

Boston M. & S. J., *Jan. 3, 1855*

MASSACHUSETTS MEDICAL SOCIETY

COMMITTEE ON MATERNAL WELFARE

Premature Toxic Separation of Placenta, with Eclampsia

A gravida II, para I, died in the sixth month of her second pregnancy, which had begun three months after the uneventful delivery of her first child. She first reported for care in the fourth month of the current pregnancy, when she was found to be normal, but six weeks later she was admitted to the hospital because of headaches, nausea, vomiting and elevated blood pressure. After two weeks she left the hospital against advice, the blood pressure being still 140 systolic, 90 diastolic, and the urine containing 340 mg. of albumin per 100 cc. During the following week the blood pressure climbed to 190 systolic, 100 diastolic, but she refused hospitalization despite the warnings of the obstetrician, who then told her to get another doctor if she would not follow his directions.

Three nights later she began to bleed by vagina, and in a few hours labor began. Under emergency circumstances the same doctor reluctantly accepted her call. She was admitted with the cervix almost fully dilated.

The membranes were ruptured artificially, and spontaneous delivery of a stillborn infant weighing 0.6 kg. (1 pound, 4 ounces) occurred without anesthesia in one hour. Blood loss during labor was estimated at 500 cc., and atony developed post partum, resulting in a blood pressure of 90 systolic (indeterminate diastolic), with a poor pulse. Transfusions were begun two hours post partum. The patient was rational and conscious but in shock, which did not respond to the blood, nasal instillation of oxygen or other measures. She was therefore given two divided doses of Levophed. Within a few minutes of the second dose, which was given almost eight hours post partum, she went into convulsions and promptly died.

No autopsy was done, but a post-mortem catheter specimen revealed an albumin of 1000 mg. per 100 cc. in the urine, which was loaded with casts.

This case was classified as a preventable death caused by premature toxic separation of the placenta and by eclampsia. However, responsibility for death lay with the patient herself and with her family. There have been a number of fatal cases of eclampsia in Massachusetts recently in which the patient refused to follow her physician's advice. This one, however, is distinguished by repeated genuine efforts to enforce orders, which were ignored. More than this, it seems, cannot be done. The physician is to be complimented upon responding to the patient's call for delivery after once declining responsibility since it is unlikely at that time that anyone could have succeeded in correcting her difficulties.

As in all cases involving hemorrhage, evidence of delay is sought. In this case two hours elapsed between the time of delivery and the first transfusion. This is perhaps the only point at which treatment was in any way inadequate. One cannot help wondering whether her state of collapse might have responded more readily if vigorous transfusions had been started immediately post partum. Admittedly, however, the subsequent post-partum convulsion, with obviously severely damaged kidneys, makes it extremely unlikely that she would have survived.

John Figgis Jewett, M.D.
Chairman

DEATHS

Gagné—Joseph A. Gagné, M.D., of Chicopee, died on November 29. He was in his seventy-fourth year.

Dr. Gagné received his degree from the University of Montreal Faculty of Medicine in 1911. He was a fellow of the American Medical Association.

He is survived by his widow, one son and six daughters.

Morrison—Gordon M. Morrison, M.D., of Boston, died on December 1. He was in his sixtieth year.

Dr. Morrison received his degree from Tufts College Medical School in 1926. He was formerly president of the American Association for Surgery of Trauma and of the Massachusetts Society of Examining Physicians, vice-president of the board of governors of the American College of Surgeons, a trustee of the Massachusetts Memorial Hospitals, secretary-treasurer of the New England Bone and Joint Society and a member of the executive council of the Boston Orthopedic Club. He was a fellow of the American Medical Association and the American College of Surgeons.

He is survived by his widow, three sons and one brother.

Mullen—Lawrence G. Mullen, M.D., of Cambridge, died on October 11. He was in his forty-seventh year.

Dr. Mullen received his degree from Tufts College Medical School in 1934. He was a member of the staff of Mount Auburn, St. Elizabeth's and Cambridge City hospitals and was a fellow of the American Medical Association.

He is survived by one son and a daughter.

Thompson—Peter H. Thompson, M.D., of Boston, died on December 1. He was in his eighty-third year.

Dr. Thompson received his degree from Tufts College Medical School in 1898, and from Harvard Medical School in 1901. He was formerly a member of the staffs of Boston City and Massachusetts General hospitals and was a fellow of the American Medical Association and a member of the American Academy of Ophthalmology and Otolaryngology and the New England Ophthalmological Society.

He is survived by his son and four grandchildren.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

Orthopedic Clinic	Date	Clinic Consultant
Haverhill	January 4	William T. Green, M.D., and Henry H. Banks, M.D.
Greenfield	January 5	Charles L. Sturdevant, M.D.
Lowell	January 6	Albert H. Brewster, M.D.
Gardner	January 9	Carter R. Rowe, M.D.
Lynn*	January 9	Daniel M. Killoran, M.D., and John J. Crowley, M.D.
Salem	January 9	Paul W. Hugenberger, M.D.
Brockton	January 12	George W. Van Gorder, M.D.
Worcester	January 13	John W. O'Meara, M.D.
Pittsfield	January 18	Edward J. Coughlin, Jr., M.D.
Fall River	January 23	David S. Grice, M.D., and Arthur W. Trott, M.D.
Springfield	January 24	James D. Fisher, M.D.
Hyannis	January 26	Paul L. Norton, M.D.

Rheumatic-Fever Clinic	Dates
North Reading	January 3, 10, 17, 24
Fitchburg	January 4, 11, 18, 25

Plastic Clinic	Held	Consultant
Eastern Massachusetts	Semi-Monthly	Bradford Cannon, M.D., and Joseph E. Murray, M.D.
Western Massachusetts	Monthly	Joseph M. Baker, M.D.

Physicians referring new patients to clinic should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

*This clinic serves Lynn, Lynnfield, Saugus, Nahant, Revere, Chelsea, Everett and Winthrop. Referrals should be made directly to the Lynn Clinic.

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR NOVEMBER, 1955

RÉSUMÉ

Disease	Nov. 1955	Nov. 1954	Seven-Year Median
Chancroid	0	4	4
Chicken pox	707	714	862
Diphtheria	1	1	6
Dog bite	737	798	789
Dysentery, bacillary	11	21	8
Encephalitis, infectious	1	1	1
German measles	49	73	62
Gonorrhea	150	178	180
Granuloma inguinale	0	0	0
Hepatitis, infectious	27	114	50*
Lymphogranuloma venereum	1	0	0
Malaria	0	0	1
Measles	13	2393	157
Meningitis, meningococcal	5	3	3
Meningitis, Pfeiffer bacillus	1	5	5
Meningitis, pneumococcal	4	0	3
Meningitis, staphylococcal	0	0	0
Meningitis, streptococcal	0	0	0
Meningitis, undetermined	8	9	5
Mumps	121	939	931
Poliomyelitis	204	98	56
Salmonellosis	45	40	11
Scarlet fever	167	192	233
Syphilis	168	120	133
Trichinosis	0	0	2
Tuberculosis, pulmonary	189	136	189
Tuberculosis, other forms	10	12	7
Typhoid fever	2	2	2
Undulant fever	1	0	2
Whooping cough	54	344	297

*Six-year median.

Comment

Diseases below the seven-year median were chicken pox, diphtheria, German measles, infectious hepatitis, measles, mumps, scarlet fever and whooping cough.

Last month infectious hepatitis was at the lowest level for November since 1951.

During November measles was at the lowest level for any month in the State's history. Mumps was at the lowest level for November since 1915.

With but one exception (1951) scarlet fever was at the lowest level for the month of November in the history of the State.

During November whooping cough also was at the lowest level for this month in the State's history.

Diseases above the seven-year median were bacillary dysentery, poliomyelitis and salmonellosis, the last two being at their highest levels for this month in the State's history.

Geographic Distribution of Certain Diseases

The following diseases were reported from the communities named:

Diphtheria: Quincy, 1.

Dysentery, amebic: Pittsfield, 1.

Dysentery, bacillary: Boston, 2; Medford, 2; Waltham, 2; Worcester, 5; total, 11.

Encephalitis, infectious: Weymouth, 1.

Hepatitis, infectious: Andover, 1; Beverly, 1; Boston, 3; Chelsea Naval Hospital, 2; Fall River, 3; Gardner, 3; Holyoke, 1; Huntington, 2; Needham, 4; Pittsfield, 1; Tewksbury State Infirmary, 3; Watertown, 1; Wellesley, 1; Wilmington, 1; total, 27.

Meningitis, meningococcal: Boston, 2; Hingham, 1; Webster, 1; Worcester 1; total, 5.

Meningitis, Pfeiffer bacillus: Springfield, 1.

Meningitis, pneumococcal: Boston, 1; Dalton, 1; Lowell, 1; West Springfield, 1; total, 4.

Meningitis, undetermined: Cambridge, 1; Fitchburg, 1; Haverhill, 1; Methuen, 1; Needham, 1; North Adams, 1; Reading, 1; Springfield, 1; total, 8.

Poliomyelitis: Abington, 2; Amherst, 1; Arlington, 3; Ashland, 4; Attleboro, 2; Barnstable, 2; Bedford, 1; Bedford Air Force Base, 1; Bellingham, 1; Bernardston, 1; Beverly, 1; Billerica, 1; Blackstone, 3; Boston, 17; Bourne, 2; Braintree, 1; Brookline, 2; Burlington, 2; Cambridge, 3; Charlton, 2; Chelsea, 3; Chicopee, 2; Cohasset, 1; Concord, 1; Danvers, 1; Dudley, 1; Eastham, 1; Edgartown, 1; Essex, 1; Everett, 3; Fairhaven, 1; Fall River, 2; Falmouth, 4; Fitchburg, 1; Framingham, 8; Hanover, 1; Hingham, 1; Holliston, 1; Hopedale, 2; Hopkinton, 3; Hubbardston, 1; Ipswich, 1; Lexington, 2; Lincoln, 2; Lowell, 1; Lynn, 4; Lynnfield, 3; Malden, 5; Mansfield, 2; Marlboro, 1; Mashpee, 1; Maynard, 1; Melrose, 1; Middleboro, 2; Middleton, 1; Milford, 1; Millis, 1; New Bedford, 2; Newton, 5; North Andover, 1; Northfield, 1; Norwood, 1; Orleans, 2; Peabody, 3; Pittsfield, 1; Quincy, 4; Needham, 1; Randolph, 3; Revere, 2; Rockland, 1; Sandisfield, 1; Somerset, 1; Somerville, 3; Southboro, 1; Springfield, 1; Stoneham, 1; Stoughton, 2; Sturbridge, 1; Swampscott, 1; Topsfield, 1; Upton, 1; Wakefield, 2; Waltham, 4; Watertown, 1; Wayland, 2; Webster, 2; Wellesley, 1; West Boylston, 1; West Bridgewater, 3; Westfield, 3; Westwood, 2; Weymouth, 2; Whitman, 1; Wilmington, 3; Winchendon, 1; Winthrop, 3; Woburn, 3; Worcester, 8; total, 204.

Psittacosis: Cheshire, 1.

Salmonellosis: Attleboro, 3; Boston, 5; Brookline, 2; Cambridge, 1; Lowell, 1; Milton, 1; Northbridge, 3; Peabody, 1; Somerville, 2; Springfield, 23; Weymouth, 3; total, 45.

Tetanus: Lawrence, 1.

Typhoid fever: Fall River, 2.

Undulant fever: Hawley, 1.

CORRESPONDENCE

PREVENTIVE CHEMOTHERAPY IN MEASLES

To the Editor: Dr. Louis Weinstein's paper in the October 20 issue of the *Journal*, on the failure of chemotherapy to prevent the bacterial complications of measles, requires, I think, a critical comment.

The essential information may be reset in the following form for clarity:

Antibiotic Treatment before Admission & Onset of Complications	Bacterial Infection at Time of Admission		
	present	absent	total present
Yes	36	94	130(27.7%)
No	42	256	298(14.1%)
Totals	78	350	428(18.2%)

The percentages have been recalculated; the author gives the rate of infection as 30.4 per cent among children receiving and 14.9 per cent among those not receiving antibiotics before admission, but it is not clear how he obtained these figures.

From these observations it is suggested that the use of antimicrobial agents may actually be associated with an increased risk of development of serious bacterial infection in measles (the inference seems to be causally associated).

Several other explanations for the observed association are possible. They rest upon the fact that the cases of measles in a hospital are a small, and presumably highly selected, sample of the cases in the community. I suppose that this selection is at least in part on the basis of severity of illness and presence of complications.

Two reasonable explanations are suggested. The first consists in a tendency of physicians to treat young or debilitated children with antibacterial agents more often than older and healthy children. If the frequency of complications is in fact higher among such children, this would have an effect in the observed direction. Secondly, the sicker children may have been more often treated with antibiotics. If the patients with severer cases have a higher risk of secondary infection, this also would produce the apparent association. Perhaps, on the other hand, some of the treated patients already had secondary infections when treatment was initiated. Dr. Weinstein states that this was not so, but one may perhaps question whether the day of onset of complicating infections can always be accurately determined from the histories of children before hospitalization.

The statement is also made that the risk of this type of complication appeared to be about three times greater at home than in the hospital, and the inference is drawn that exposure to pathogens is greater in the home than in the hospital. This observation also is readily explained by the selection of patients. Presumably, the secondary infections among those not subsequently hospitalized, and hence not coming to the author's attention, were fewer, since it is likely that many were hospitalized *because* of the complicating infections. In the past it has been thought that hospitalization enhanced rather than reduced the risk of exposure to new bacterial pathogens, to which the child had not become immune. This will depend on the adequacy of isolation in the hospital, but these data do not constitute proof of the greater hazard at home.

Before concluding that prophylactic antibiotics are of no value, and even possibly harmful, better evidence should be sought. The best opportunity to settle the question might be afforded by an institutional outbreak of measles in which properly randomized groups might be chosen for antibacterial treatment, with suitable controls. I doubt whether an answer can be obtained with the approach taken in this study, because of the factors of selection involved.

Philip E. Sartwell, M.D.

Baltimore, Maryland

Dr. Sartwell's letter was submitted to Dr. Weinstein, who offers the following reply:

To the Editor: I agree with Dr. Sartwell that the patients described in my paper were a somewhat selected group. This is so stated in the summary and conclusions of the paper: "Despite the fact that the patients described in this paper are a somewhat selected group and represent only a small fraction of cases of measles treated by physicians at home . . . ." I cannot agree, however, that they were "highly selected." As a matter of fact, the ratio of patients with uncomplicated to complicated cases entering the hospital indicates very little selection in favor of the latter. Seventy-eight of the 428 patients had bacterial infections at the time of admission; this includes both treated and untreated persons. This makes approximately 18 per cent complicated cases, or a ratio of more than 4 uncomplicated cases to 1 that is complicated.

Dr. Sartwell's second explanation is not "reasonable" in view of the fact that none of the patients who were studied were debilitated. This type of criticism is unacceptable unless the critic has personally observed the patients who were described. Furthermore, I can assure Dr. Sartwell that the use of antibiotics in this community is very little influenced by the presence or absence of debilitation. The fact that young patients with measles tend to be given antibacterial agents more frequently than older ones in no way raises any serious questions concerning the validity of the published results. If young children with measles are the ones in whom secondary bacterial infections are most likely to develop, they are the ones who need prophylaxis the most; the data indicate clearly that, regardless of any factors of selection, the appearance of bacterial infection was not inhibited by the use of antimicrobial drugs. Furthermore, it has been shown in our clinic that the young child with bronchopulmonary disease, like the child with measles, is most susceptible to the development of *superinfection when given an antibiotic.* That this is so is borne out by our experience in the treatment of secondary infections that occurred for the first time while children with measles were in the hospital. I think it is this special predisposition to superinfection during antimicrobial therapy that accounts for the relatively high number of infections in patients with measles given chemoprophylaxis.

Several remarks are called for in answer to the statements in Dr. Sartwell's second explanation. In the first place, the "severe" cases of measles—I presume this means the patient with high fever or an extensive rash, or both—do not necessarily have a higher risk of secondary infection than the mild ones. Secondly, the remainder of the remarks in this explanation are pure conjecture, as indicated by the word "perhaps" with which they begin. These patients did not have secondary infection before treatment at home as far as could be ascertained after very careful investigation of this point. Furthermore, in a great many cases, treatment with antibacterial agents was started during the early prodromal phase of the disease when the physician was not aware that the patient was in the early stages of measles and thought that he was treating a bacterial infection. Secondary infections during the pre-eruptive phase of rubeola are very uncommon in our experience.

The suggestion that the best way to approach this problem would be to study an institutional outbreak of measles is a good one and obviously would yield the most accurate answers. To do this properly, however, would mean that no attempt would be made to stop the spread of an epidemic by the proper use of modifying or preventive doses of gamma globulin; otherwise, there would be too few cases to study. I doubt very much whether such an approach even for the purpose of obtaining the more accurate data from "properly randomized" groups is justifiable in the face of the risk of encephalitis with its 10 per cent incidence of death and 65 per cent incidence of neurologic and psychologic residua.

Finally, it is important to point out that measles is not the only situation in which chemoprophylaxis has been found to be of no value. This has also been found to be true in "respiratory" poliomyelitis and in elective surgery in other hospitals.

Louis Weinstein, M.D.

Boston

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

V. Mesenterica superior: contribuição anatômica às anastomoses cirúgicas com o sistema cava inferior. By Salomão Kelner. Thesis. 8°, paper, 131 pp., with 30 illustrations. Recife, Brasil. 1953.

This thesis was presented for the doctorate at the University of Recife. The study is based on the dissection of 30 bodies. The author was investigating the possibilities of anastomosing the superior mesenteric vein with the vena cava inferior and with the vena renalis sinistra. There is a descriptive table of the anatomic conditions found in the 30 dissections. A list of references is appended to the text.

Einführung in die biologische Registriertecknik. By Dr. Med. Herbert Klensch, lecturer, Physiologisches Institut der Universität Bonn. 8°, cloth, 222 pp., with 142 illustrations. Stuttgart: Georg Thieme, 1954. DM 33. $7.85. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

The author deals with the methods of registering biologic data. Some of the material is of definite medical interest: blood pressure, radioactive substances, tachography and artificial stimulation of biologic objects. There is a bibliography of 421 references and an index of subjects.

Review of Medical Microbiology. By Ernest Jawetz, Ph.D., M.D., professor of bacteriology and lecturer in medicine and pediatrics, University of California School of Medicine; Joseph L. Melnick, Ph.D., professor of epidemiology, Yale University School of Medicine; and Edward A. Adelberg, Ph.D., assistant professor of bacteriology, University of California. 4°, paper, 360 pp., with 92 illustrations. Los Altos: Lange Medical Publications, 1954. $4.50.

This is the first of a summary to be published every two years of the existing knowledge of the various aspects of medical microbiology. The book is written primarily for the student, house officer and practicing physician. The material is well organized, and there is a good index. The book should prove useful to all persons interested in the subject.

The Causes and Treatment of Backwardness. By Cyril Burt, D.Sc., Hon.Litt.D., Hon.LL.D., fellow of the British Academy and honorary fellow, Jesus College, Oxford. 8°, cloth, 128 pp. New York: Philosophical Library, 1953. $3.85.

This monograph on backwardness in school children was originally printed, as a small volume, by the boys of a school in England and was intended primarily for psychologists, educators and research workers. The second edition has been revised, material added, and the text made available for the classroom teacher. The chapters deal with methods of investigation, environmental factors and factors of personality; physical, intellectual, emotional and moral. The final chapter presents a summary of the subject, and there is an index. The printing and binding were done in Great Britain, and the publishing is excellent. This small book should be available to all persons interested in the subject.

Elements of Surgical Diagnosis. Tenth edition, revised by Sir Cecil Wakeley, Bt., K.B.E., C.B., LL.D., M.Ch., D.Sc., F.R.C.S., F.A.C.S., fellow of King's College, London, president of the Royal College of Surgeons, senior surgeon, King's College Hospital, director of surgical studies and lecturer in surgery, King's College Hospital Medical School, surgeon to the Royal Masonic Hospital and Belgrave Hospital for Children, consulting surgeon to the Royal Navy, Hunterian Professor, Royal College of Surgeons of England, and examiner in surgery to the University of Cambridge. 12°, cloth, 586 pp., with 19 plates. New York: Paul B. Hoeber, Incorporated, 1954. $7.50.

Seven years having elapsed since the last edition of this manual was published, Mr. Wakeley has completely revised the text to bring it up to date. All the chapters have been rewritten, and new ones incorporated, including those on surgery of the chest and brain and spinal cord. There is a good index. The printing was done in Great Britain; the publishing is excellent.

Handbook of Emergency Toxicology: A guide for the identification, diagnosis and treatment of poisoning. By Sidney Kaye, M.Sc., toxicologist, office of the chief medical examiner, Commonwealth of Virginia, associate professor of legal medicine, Medical College of Virginia, attending toxicologist, Veterans Administration Hospital, Richmond, Virginia, toxicologist, research and development group (training), University of Virginia, Department of Medicine. 8°, cloth, 303 pp., with 12 figures. Springfield, Illinois: Charles C Thomas, 1954. $5.75. (*American Lecture Series*, No. 214.)

This is an important book for the physician for ready reference in cases of emergency. The text is in three sections: symptoms and signs, lethal doses, antidotes and analysis; commercial sources of poisons and poisons generally found in household articles; and an alphabetical list of poisons. There is a good index. The book should be in all medical libraries as a reference source.

The Human Brain in Sagittal Section. By Marcus Singer, Ph.D., professor of zoology, Cornell University; and Paul I. Yakovlev, M.D., assistant clinical professor of neurology, Harvard Medical School. 8°, cloth, 81 pp., with 46 plates. Springfield, Illinois: Charles C Thomas, 1954. $7.75.

The authors have provided a beautiful and valuable atlas on the minute structure of the brain. There is a comprehensive index of 25 pages. The publishing is excellent. The atlas should be in all collections on neurology.

Ciba Foundation Symposium on Hypertension: Humoral and neurogenic factors. Edited by G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch., and Margaret P. Cameron, M.A., A.B.L.S., assisted by Joan Etherington. 8°, cloth, 294 pp., with 73 illustrations. Boston: Little, Brown and Company, 1954. $6.75.

During this conference 21 papers were read on various aspects of hypertension, some of them experimental. Lists of references are appended to the papers, and there are indexes of authors and subjects. The book and the series should be in all medical libraries.

Hernia: The pathologic anatomy of the more common hernias and their anatomic repair. By Chester B. McVay, M.D., Ph.D., clinical professor of surgery and associate professor of anatomy, University of South Dakota School of Medical Sciences, and surgeon, Yankton Clinic, Yankton, South Dakota. 4°, cloth, 40 pp., with 19 plates. Springfield, Illinois: Charles C Thomas, 1954. $4.75.

This is a diagrammatic presentation of the operations for diaphragmatic, epigastric, umbilical, inguinal, femoral, incisional, lumbar and pelvic hernias.

Shock and Circulatory Homeostasis. Edited by Harold D. Green, M.D., professor of physiology and pharmacology and associate in internal medicine, Bowman Gray School of Medicine, Wake Forest College, Winston-Salem, North Carolina. 8°, cloth, 230 pp., with 61 illustrations. New York: Sponsored by the Josiah Macy, Jr. Foundation, 1954. $3.50. (Transactions of the Third Conference, September 14, 15, and 16, 1953. Princeton, New Jersey.)

Three subjects were discussed at this meeting: experiences with shock in the Korean war; reflex factors in the regulation of the circulation; and functional properties of blood vessels. Lists of references are appended to the papers, and there is a good index.

Metabolic Interrelations with Special Reference to Calcium. Edited by Edward C. Reifenstein, Jr., director of biologic and therapeutic research, Schering Corporation, Bloomfield, New Jersey. 8°, cloth, 386 pp., with 126 illustrations and 42 tables. New York: Sponsored by the Josiah Macy, Jr., Foundation, 1954. $5.00. (Transactions of the fifth conference, January 5 and 6, 1953.)

Twenty-four papers were read at this conference. There is a cumulative index of the five congresses, 1949-1953.

Administrative Medicine: Transactions of the Second Conference December 8, 9, and 10, 1953, Princeton, N. J. Edited by George S. Stevenson, M.D., national and international consultant, National Association for Mental Health. New York: Josiah Macy, Jr., Foundation, 1954. $3.00.

The topics considered at this second conference included major components of administrative medicine, home-care programs, the health services of the Department of Health of Scotland and home-care studies.

The Microphysical World. By William Wilson, Ph.D., (Leipzig), D.Sc. (London), F.R.S., fellow of King's College, London, and professor emeritus of physics, University of London. 16°, cloth, 216 pp., with 12 illustrations. New York: Philosophical Library, 1954. $3.75.

This small book discusses the molecule and the atom.

Let's Eat Right to Keep Fit. By Adelle Davis, M.S., consulting nutrionist. 8°, cloth, 322 pp. New York: Harcourt, Brace and Company, 1954. $3.00.

The author, in this book written for the laity, presents the fundamentals of dietetics and nutrition in an interesting narrative form. A table of food analysis is appended to the text, and there is a good index.

Answer to Job. By C. J. Jung. Translated from the German by R. F. C. Hull. 12°, cloth, 194 pp. London: Routledge and Kegan, 1954. 12s.6d.

NONCLINICAL NOTES

NEW STATE ASSOCIATION FOR MENTAL HEALTH

The Massachusetts Association for Mental Health and the Mental Health Fund will join forces to form a new organization. Under the leadership of the Reverend Robert G. Metters, the organization will be called Massachusetts Association for Mental Health, Inc.

Headquarters for the association will remain at 41 Mt. Vernon Street, and the fund-raising unit, formerly at 164 Newbury Street, will be located at 89 Franklin Street.

NOTICES

ANNOUNCEMENT

Dr. Thomas S. Sappington announces the removal of his office to Suite 301, Elevator No. 1, 1025 Connecticut Avenue, Washington 6, D.C.

FREE HOSPITAL FOR WOMEN

The teaching ward rounds at the Free Hospital for Women will be held on the ward of South 2 every Saturday morning at 10:30 a.m. All interested physicians are invited to attend.

SOLDIERS' HOME STAFF MEETING

A professional-staff meeting of the Soldiers' Home, Chelsea, will be held in the auditorium of the Quigley Memorial Hospital on Wednesday, January 4, at 7:15 p.m. Dr. J. Englebert Dunphy will speak on the subject "Wound Healing: A new perspective."

Members of the medical profession are invited.

MASSACHUSETTS INSTITUTE OF TECHNOLOGY SYMPOSIUM

The Medical Department and the Coaches Association of the Massachusetts Institute of Technology will present a symposium entitled "Physiologic Effects of Exercise versus Activity" in the Kresge Auditorium, Massachusetts Institute of Technology, on Tuesday, January 10, at 8:15 p.m. The program is as follows:

Loafers' Muscles and Loafers' Heart. Dr. Wilhelm Raab.
Role of Inactivity in the Production of Disease. Dr. Hans Kraus.
Exercise, Appetite and Fat Metabolism. Dr. Jean Mayer.

AMERICAN DIETETIC ASSOCIATION

The Second International Congress of Dietetics will be held at the Congress Palace of Esposizione Universale Roma, Rome, Italy, September 10-14.

The program, which is divided into four main sections, will include such subjects as recent findings of nutritional research, methods of education in nutrition, principles and problems of feeding large numbers of people and problems of training dietitians.

Further information may be obtained from the American Dietetic Association, 620 North Michigan Avenue, Chicago, Illinois.

SOCIETY MEETINGS AND CONFERENCES

JANUARY 4–26. Consultation Clinics for Crippled Children in Massachusetts. Page 1177.
JANUARY 4. Free Hospital for Women. Notice above.
JANUARY 9. New England Cardiovascular Society. Page 1135, issue of December 22.
JANUARY 9–14, 1956. Pan American Congress of Ophthalmology. Page 944, issue of November 24.
JANUARY 10. Harvard Medical Society. Page 1135, issue of December 22.
JANUARY 10. Massachusetts Institute of Technology Symposium. Notice above.
JANUARY 10. Soldiers' Home Staff Meeting. Notice above.
JANUARY 13, 20 and 27 and FEBRUARY 3, 1956. Yale University School of Medicine, Yale-New Haven Medical Center. Page 1092, issue of December 15.
JANUARY 16, 1956. Hartford Medical Society. Page 708, issue of October 20.
JANUARY 16, FEBRUARY 6, MARCH 5 and APRIL 2, 1956. Fried Lecture Series. Page 535, issue of September 22.
JANUARY 20–27, 1956. Fifth Panamerican Congress of Gastroenterology. Page 746, issue of October 27.
JANUARY 25, FEBRUARY 29, MARCH 21 and APRIL 25, 1956. Massachusetts Heart Association. Page 623, issue of October 16.
JANUARY 25, MARCH 21 and APRIL 26, 1956. Phi Delta Epsilon Fraternity Graduate Club Program. Page 118, issue of July 21.
JANUARY 30–FEBRUARY 8, MARCH 19–28 and JUNE 4–13, 1956. Army Medical Service Postgraduate Course. Page 84, issue of July 14.
FEBRUARY 2–22. Atlanta Graduate Medical Assembly. Page 1136, issue of December 22.
FEBRUARY 13–16. American College of Surgeons. Page 1136, issue of December 22.
FEBRUARY 15, MARCH 28 and APRIL 18, 1956. Greater Boston Medical Society. Page 208, issue of August 4.
MARCH 19–22, 1956. American Academy of General Practice. Page 1092, issue of December 15.
MARCH 24 and 25, 1956. American Psychosomatic Society. Page 260, issue of August 11.
MAY 7, 1956. Postgraduate Medical Institute. Page 487, issue of September 15.